CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being transmitted therewith) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dennis P. Tramaloni
(Print Name)

Date: April 12, 2004

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1614

Alexander Alanine, et al.

Serial No.: 10/626,681

Filed: July 24, 2003

For: **BENZODIOXOLE DERIVATIVES**

TRANSMITTAL OF CERTIFIED COPY

April 12, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

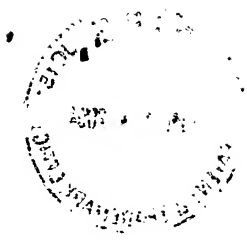
Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	02016831.6	July 29, 2002

Respectfully submitted,

Dennis P. Tramaloni
Attorney for Applicant
Reg. No. 28542
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
Phone: (973) 235-4475

DPT/bah
Enclosure
54020



Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02016831.6

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Europäisches Patentamt | European Patent Office | Office européen des brevets

Anmeldung Nr:
Application no.: 02016831.6
Demande no:

Anmeldetag:
Date of filing: 29.07.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

F. HOFFMANN-LA ROCHE AG

4070 Basel
SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel 2,2-diphenyl-benzodioxole derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D317/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

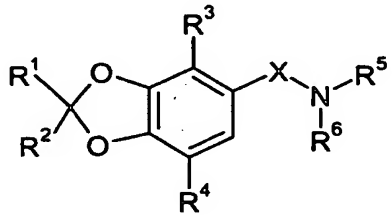
F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 21237

Novel 2,2-Diphenyl-benzodioxole Derivatives

The present invention is concerned with novel 2,2-diphenyl-benzodioxole derivatives, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The active compounds of the present invention are useful in treating obesity and other disorders.

In particular, the present invention relates to compounds of formula (I):



(I)

wherein

R^1 and R^2 are independently unsubstituted phenyl, or phenyl which is mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, perfluoro-lower alkyl, alkanoyl, cyano or halogen;

R^3 and R^4 are independently hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, perfluoro-lower alkyl, alkanoyl or cyano;

R^5 is hydrogen or lower alkyl;

R^6 is phenyl or phenyl lower alkyl, wherein the phenyl moiety may optionally be mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxy, halogen, perfluoro-lower alkyl, hydroxy, alkanoyl or cyano; or

R^5 and R^6 together with the nitrogen atom to which they are attached form a 5-, 6- or 7-membered monocyclic or a 9- or 10-membered bicyclic, saturated or unsaturated heterocyclic ring which may optionally contain one or two further heteroatoms independently selected from O, N and S, said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxycarbonyl, hydroxy lower alkyl, alkanoyl, amino lower alkyl, hydroxy, lower alkoxy, halogen, perfluoro-lower alkyl, cyano, heteroaryl, or by phenyl or phenyl lower alkyl, wherein the phenyl moiety may optionally be mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxy, halogen, perfluoro-lower alkyl, hydroxy, alkanoyl or cyano;

X is $-CH_2-$, $-C(O)-$ or $-SO_2-$;

and pharmaceutically acceptable salts thereof.

Two different subtypes of cannabinoid receptors (CB_1 amd CB_2) have been isolated and both belong to G protein coupled receptor superfamily. An alternative spliced form of CB_1, CB_{1A}, has also been described, but it did not exhibit different properties in terms of ligand binding and receptor activation than CB_1 (D.Shire, C. Carrillon, M. Kaghad, B. Calandra, M. Rinaldi-Carmona, G. Le Fur, D. Caput, P. Ferrara, J. Biol. Chem. 270 (8) (1995) 3726-31). The CB_1 receptor is mainly located in the brain, whereas the CB_2 receptor is predominately distributed in the peripherie primarily localized in spleen and cells of the immune system (S. Munro, K.L. Thomas, M. Abu-Shaar, Nature 365 (1993) 61-61). Therefore in order to avoid side effects a CB_1-selective compound is desirable.

Δ^9-tetrahydrocannabinol (Δ^9-THC) is the principal psychoactive compound in the Indian hemp (Y. Gaoni, R. Mechoulam, J. Am. Chem. Soc., 86 (1964) 1646), *canabis savita* (marijuanan), which is used in medicine since ages (R. Mechoulam (Ed.) *in "Cannabinoids as therapeutic Agents"*, 1986, pp. 1-20, CRC Press). Δ^9-THC is a non-selective $CB_1/_2$ receptor agonist and is available in the USA as dronabinol (marinol®) for the alleviation of cancer chemotherapy-induced emesis (CIE) and the reversal of body weight loss experienced by AIDS patients through appetite stimulation. In the UK Nabolinone (LY-109514, Cesamet®), a synthetic analogue of Δ^9-THC, is used for CIE (R. G. Pertwee, Pharmaceut. Sci. 3 (11) (1997) 539-545, E. M. Williamson, F. J. Evans, Drugs 60 (6) (2000) 1303-1314).

Anandamide (arachidonylethanolamide) was identified as the endogenous ligand (agonist) for CB_1 (R.G. Pertwee, Curr. Med. Chem., 6 (8) (1999) 635-664;W.A. Devane, L. Hanus, A. Breuer, R.G. Pertwee, L.A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger, R. Mechoulam, Science 258 (1992) 1946-9). Anandamide and 2-arachidonoylglycerol (2-AG) modulate at the presynaptic nerve teminal negatively adenylate cyclase and voltage-sensitive Ca^{2+} channels and activates the inwardly rectifying K^+ channel (V. Di Marzo, D. Melck, T. Bisogno, L. De Petrocellis, Trends in Neuroscience 21 (12) (1998) 521-8), thereby affecting neurotransmitter release and/or action, which decreases the release of neurotransmitter (A. C. Porter, C.C. Felder, Pharmacol. Ther., 90 (1) (2001) 45-60).

Anandamide as Δ^9-THC also increases feeding through CB_1 receptor-mediated mechanism. CB_1 selective antagonists block the increase in feeding associated with administration of anandamide (C.M. Williams, T.C. Kirkham, Psychopharmacology 143 (3) (1999) 315-317; C. C. Felder, E. M. Briley, J. Axelrod, J. T. Simpson, K. Mackie, W. A. Devane, Proc. Natl. Acad. Sci. U. S. A. 90 (16) (1993) 7656-60) and caused appetite suppression and weight loss (G. Colombo, R. Agabio, G. Diaz, C. Lobina, R. Reali, G. L. Gessa, Life Sci. 63 (8) (1998) L113-PL117).

Leptin is the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. Following temporary food restriction, CB1 receptor knockout mice eat less than their wild-type littermates, and the CB1 antagonist SR141716A reduces food intake in wild-type but not knockout mice. Furthermore, defective leptin signaling is associatedd with elevated hypothalamic, but not cerebellar, levels of endocannabinoids in obese db/db and ob/ob mice and Zucker rats. Acute leptin treatment of normal rats and ob/ob mice reduces anandamide and 2-arachidonoyl glycerol in the hypothalamus. These findings indicate that endocannabinoids in the hypothalamus may tonically activate CB1 receptors to maintain food intake and form part of the neural circuitry regulated by leptin (V. Di Marzo, S. K. Goparaju, L. Wang, J. Liu, S. Bitkai, Z. Jarai, F. Fezza, G. I. Miura, R. D. Palmiter, T. Sugiura, G. Kunos, Nature 410 (6830) 822-825).

SR-141716A, a CB1 selective antagonist / inverse agonist is undergoing currently phase III clinical trials for the treatment of obesity. In a double blind placebo-controlled study, at the doses of 5, 10 and 20 mg daily, SR 141716 significantly reduced body weight when compared to placebo (F. Barth, M. Rinaldi-Carmona, M. Arnone, H. Heshmati, G.

Le Fur, *"Cannabinoid antagonists: From research tools to potential new drugs."* Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001).

Other compounds which have been proposed as CB1 receptor antagonists respectively inverse agonists are aminoalkylindols (AAI; M. Pacheco, S. R. Childers, R. Arnold, F. Casiano, S. J. Ward, J. Pharmacol. Exp. Ther. 257 (1) (1991) 170-183), like 6-bromo- (WIN54661; F. M. Casiano, R. Arnold, D. Haycock, J. Kuster, S. J. Ward, NIDA Res. Monogr. 105 (1991) 295-6) or 6-iodopravadoline (AM630, K. Hosohata, R. M. Quock, R.M; Hosohata, T. H. Burkey, A. Makriyannis, P. Consroe, W. R. Roeske, H. I. Yamamura, Life Sci. 61 (1997) 115 – 118; R. Pertwee, G. Griffin, S. Fernando, X. Li, A. Hill, A. Makriyannis, Life Sci. 56 (23-24) (1995) 1949-55). Arylbenzo[b]thiophene and benzo[b]furan (LY320135, C. C. Felder, K. E. Joyce, E. M. Briley, M. Glass, K. P. Mackie, K. J. Fahey, G. J. Cullinan, D. C. Hunden, D. W. Johnson, M. O. Chaney, G. A. Koppel, M. Brownstein, J. Pharmacol. Exp. Ther. 284 (1) (1998) 291-7) disclosed in WO9602248, US5596106, 3-alkyl-(5,5-diphenyl)imidazolidinediones (M. Kanyonyo, S. J. Govaerts, E. Hermans, J. H. Poupaert, D. M. Lambert, Bioorg. Med. Chem. Lett. 9 (15) (1999) 2233 – 2236.) as well as 3-alkyl-5-arylimidazolidinediones (F. Ooms, J. Wouters, O. Oscaro. T. Happaerts, G. Bouchard, P.-A. Carrupt, B. Testa, D. M. Lambert, J. Med. Chem. 45 (9) (2002) 1748-1756) are known to antagonize the CB_1 receptor respectively act as an inverse agonist on the hCB_1 receptor. WO0015609 (FR2783246-A1), WO0164634 (FR2805817-A1), WO0228346, WO0164632 (FR2805818-A1), WO0164633 (FR2805810-A1) disclosed substituted 1-bis(aryl)methyl-azetidines derivatives as antagonists of CB_1. In WO0170700 4,5-dihydro-1H-pyrazole derivatives are described as CB_1 antagonists. In several patents bridged and non-bridged1,5-diphenyl-3-pyrazolecarboxamide derivatives are disclosed as CB_1 antagonists/inverse agonists (WO0132663, WO0046209, WO9719063, EP658546, EP656354, US5624941, EP576357, US3940418).

It is an object of this invention to provide selective, directly acting CB1 receptor antagonists respectively inverse agonists. Such antagonists / inverse antagonists are useful in medical therapy, particularly in the treatment and/or prevention of diseases which are associated with the modulation of CB1 receptors.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to six, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, preferably to chlorine and fluorine.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms.

The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to six carbon atoms, preferably one to four carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like.

The term "alkoxy" refers to the group R'-O-, wherein R' is alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is lower-alkyl. Examples of lower-alkoxy groups are e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and hexyloxy, with methoxy being especially preferred.

The term "lower alkoxycarbonyl" refers to the group R'-O-C(O)-, wherein R' is lower alkyl.

The term "perfluoro-lower alkyl" refers to a lower alkyl group wherein all of the hydrogens of the lower alkyl group are substituted or replaced by fluoro. Among the preferred perfluoro-lower alkyl groups are trifluoromethyl, pentafluoroethyl and heptafluoropropyl, with trifluoromethyl being especially preferred.

The term "alkanoyl" refers to a group C(O)-R wherein R is hydrogen or lower alkyl. Examples of alkanoyl groups are formyl, acetyl, propionyl and the like.

The term "phenyl-lower alkyl" refers to a phenyl group which is attached to the remainder of the molecule via a lower alkylene group, such as methylene, ethylene propylene or butylene, preferably methylene and ethylene.

The term "amino lower alkyl" refers to a lower alkyl radical substituted with an amino group.

The term "heteroaryl" refers to an aromatic monovalent mono- or poly-carbocyclic radical having at least one heteroatom selected from N, O and S. Examples of heteroaryl groups are pyridinyl, pyrazinyl and pyrimidinyl. Such heteroaryl residues may optionally be mono-, di-, or tri-substituted, independently, by lower alkoxy, lower alkyl, perfluoro-lower alkyl, cyano and alkanoyl, preferably by halogen and perfluoro-lower alkyl.

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, salicylic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts with acids are formates, maleates, citrates, hydrochlorides, hydrobromides and methanesulfonic acid salts, with hydrochlorides being especially preferred.

In a preferred embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^1 and R^2 are independently phenyl, which is mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, perfluoro-lower alkyl, alkanoyl, cyano or halogen; preferable lower alkyl substituents of phenyl residues R^1 and R^2 are lower alkyl, such as methyl, lower alkoxy, such as methoxy, and halogen, such as fluoro and chloro. Preferable R^1 and R^2 is phenyl which is mono- or di-substituted by halogen, preferably fluoro or chloro, or lower alkoxy, preferably methoxy.

In another preferred embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^3 and R^4 are independently hydrogen, hydroxy or halogen, such as fluoro, chloro or bromo. Preferred substituents R^3 and R^4 are hydrogen, and fluoro.

In another preferred embodiment, the present invention relates to a compound of formula (I) as defined above, wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a 5-, 6- or 7-membered monocyclic or a 9- or 10-membered bicyclic, saturated or unsaturated heterocyclic ring which may optionally contain one or two further heteroatoms independently selected from O and N, said heterocyclic ring being optionally mono- or di-substituted, independently, by lower alkyl, lower alkoxycarbonyl, hydroxy lower alkyl, alkanoyl, hydroxy, or by phenyl or phenyl lower alkyl, wherein the phenyl moiety may optionally be mono- or di- substituted, independently, by lower alkyl, lower alkoxy, halogen or perfluoro-lower alkyl.

Preferable heterocyclic rings formed by R^5 and R^6 together with the nitrogen atom to which they are attached are piperazinyl, morpholino, piperidinyl, piperidin-4-one, pyrrolidinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 1,2,3,6-tetrahydro-pyridinyl, [1,4]-diazepanyl and 1,4-dioxa-8-aza-spiro[4.5]dec-8-yl, with piperazinyl, morpholino and piperidinyl being especially preferred. Most preferable heterocyclic ring formed by R^5 and R^6 together with the nitrogen atom to which they are attached is piperidinyl.

The heterocyclic rings formed by R^5 and R^6 together with the nitrogen atom to which they are attached are preferably mono- or di-substituted, independently, by methyl propyl, ethoxycarbonyl, hydroxymethyl, formyl, hydroxy, unsubstituted pyrazinyl, unsubstituted pyridinyl, pyridinyl disubstituted by chloro and/or trifluoromethyl; or by phenyl or phenyl methyl, wherein the phenyl moiety may optionally be mono- or di- substituted, independently, by methyl, methoxy, chloro, fluoro and/or trifluoromethyl.

In still another preferred embodiment, the present invention relates to a compound of formula (I) as defined above, wherein X is –C(O)– or $–SO_2–$.

Preferred compounds of general formula (I) are those selected from the group consisting of:

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine,

1-(4-Chloro-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

1-(2,3-Dimethyl-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

1-(2,4-Dichloro-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(3-chloro-phenyl)-piperazine,

4-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-morpholine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-phenyl-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-pyrrolidine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(3-methoxy-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-methoxy-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-methoxy-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-chloro-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-fluoro-phenyl)-piperazine,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid phenethyl-amide,

1-Benzo[1,3]dioxol-5-yl-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

4-Benzyl-1-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine,

2-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid benzyl-methyl-amide,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid benzylamide,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-methyl-[1,4]diazepane,

1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-[1,4]diazepane,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid phenylamide,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid [2-(4-methoxy-phenyl)-ethyl]-amide,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-methyl-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine,

4-(4-Chloro-phenyl)-1-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-1,2,3,6-tetrahydro-pyridine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-phenyl-1,2,3,6-tetrahydro-pyridine,

racemic 1-[2-(2-Chloro-phenyl)-2-(4-methoxy-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(2-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(2-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

1-[2,2-Bis-(4-chloro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Fluoro-phenyl)-2-phenyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Methoxy-phenyl)-2-phenyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine,

racemic 1-[2-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(2,4-Dichloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

1-[2,2-Bis-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(3-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-(2-chloro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(3-hydroxy-pyrrolidin-1-yl)-methanone,

4-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbaldehyde,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-hydroxymethyl-piperidin-1-yl)-methanone,

(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-isopropyl-piperazin-1-yl)-methanone,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidin-4-one,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-hydroxy-piperidin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-pyrrolidin-1-yl-methanone,

racemic 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidine-3-carboxylic acid ethyl ester,

[4-(5-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-m-tolyl-piperazin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-o-tolyl-piperazin-1-yl)-methanone,

racemic 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidine-2-carboxylic acid ethyl ester,

[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

racemic (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(3-hydroxymethyl-piperidin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone,

(4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone, and

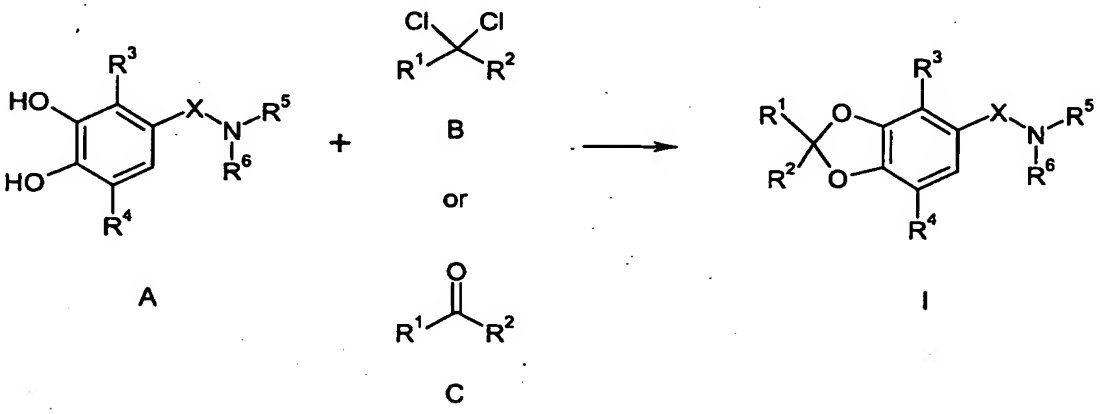
1-(2,2-Diphenyl-benzo[1,3]dioxol-5-ylmethyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine.

The present invention also relates to a process for the manufacture of compounds of formula (I) as defined above. The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the Examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by

methods analogous to the methods given below or in the Examples or by methods known in the art.

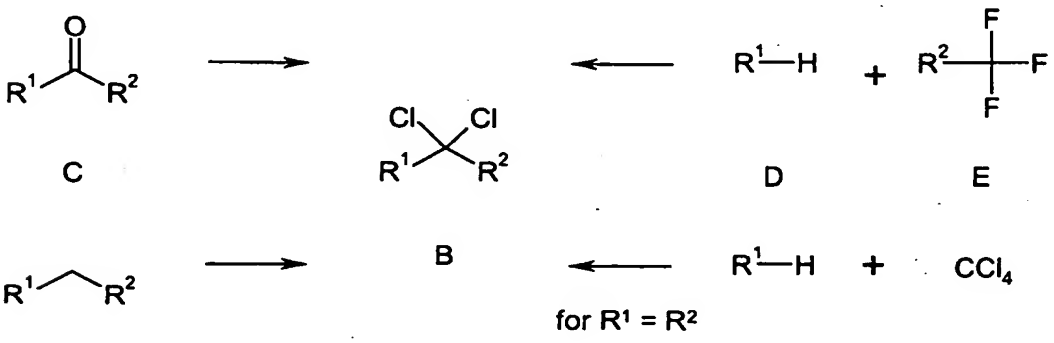
The compound of formula (I) where R^1 to R^6 and X are as previously defined may be prepared using the general methods depicted in Scheme 1 as further described below.

Scheme 1:



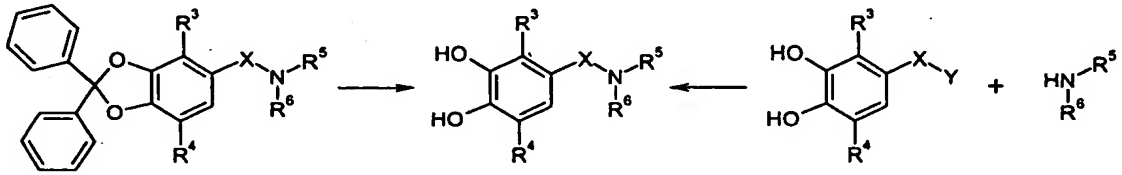
According to scheme 1 a katechol intermediate of formula A can be ketalized with a bis-substituted dichloromethane derivative of formula B in an inert solvent (e.g. toluene or pyridine) or neat with or without the presence of a base (e.g. pyridine) at elevated temperature (e.g. >100°C) to yield product I. Alternatively compound of formula (I) may be prepared by reacting the katechol intermediate of formula A with a ketone of formula C at elevated temperature (e.g. >150°C) neat or in an inert solvent (e.g. toluene) with or without the removal of water by destillation, azeotropic destillation or addition of drying agents (e.g. molecular sieves or 2,2-dimethoxypropane) by methods known in the art (see e.g. T. R. Kelly, A. Szabados, Y.-J. Lee, J. Org. Chem. 62 (2) (1997) 428). Compounds of formula (I) wherein X is $-CH_2-$ can also be obtained by reduction of a corresponding compound of formula (I) wherein X is –CO– by means known in the art.

Scheme 2:



The bis-substituted dichloromethane derivatives of formula B can be easily prepared by methods known in the art from the corresponding ketone by reaction with thionyl chloride in the presence of DMF or another N-formylated agent, by electrophylic aromatic substitution of the trifluoromethyl derivative E with a benzene derivative of formula D in the presence of aluminium trichloride in dichloro ethane (e.g. R. K. Ramchandani, R. D. Wakharkar, A. Sudalai, Tetrahedron Lett. 37 (23) (1996) 4063), by chlorination of a bisarylmethane derivative (e.g. US 5578737 or W. Deuschel, Helv. Chim. Acta 34 (1951) 2403) or in case of symmetrically bis-substituted dichloromethan derivatives of formula B by electrophilic aromatic substitution of a benzene derivative with tetrachloromethane in the presence of an lewis acid (e.g. $AlCl_3$) in an inert solvent (e.g. 1,2-dichloroethane) (see e.g. J. P. Picard, C. Kearns, Can. J. Res. 28 (1950) 56).

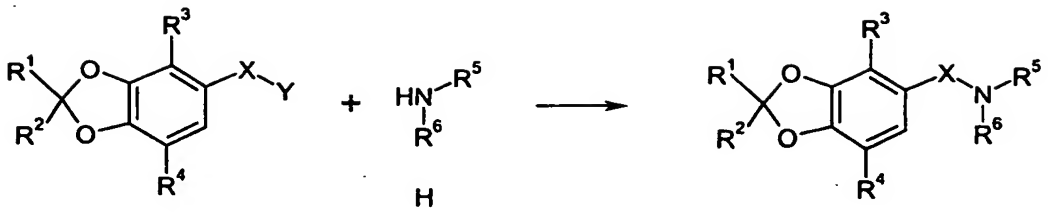
Scheme 3:



Ia A F

Katechols of formula A can be easily prepared from the corresponding diphenylmethylene protected ketals of formula (Ia) by treatment with an acid (e.g. trifluoroacetic acid) in a suitable inert solvent (e.g. methylene chloride). Alternatively a katechol derivative of formula F can be coupled with an appropriate amine in an suitable inert solvent (e.g. DMF, methylene chloride, pyridine or THF) in the presence of a base (e.g. triethyl amine). Either the corresponding acid chlorides (X=CO, Y=Cl) respectively the corresponding sulfonyl chlorides ($X=SO_2$, Y=Cl) or the corresponding carboxylic acids (X=CO, Y=OH) after activation with an appropriate coupling agent (e.g. carbonyldiimidazole) are used for the preparation of katechols of formula A by methods known in the art. Compounds of fotmula (A) wherein X is $-CH_2-$ can be obtained by reduction of a corresponding compound of formula (A) wherein X is –CO– by means known in the art.

Scheme 4:



G H I

Compounds of formula G can be coupled with an appropriate amine in a suitable inert solvent (e.g. DMF, methylene chloride, pyridine or THF) in the presence of a base (e.g. triethyl amine) to yield katechols of formula (I). Either the corresponding acid chlorides (X=CO, Y=Cl) respectively the corresponding sulfonyl chlorides ($X=SO_2$, Y=Cl) or the corresponding carboxylic acids (X=CO, Y=OH) after activation with an appropriate coupling agent (e.g. carbonyldiimidazole) are used for the preparation of katechols of formula (I) by methods known in the art.

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

Some compounds of formula (I) may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediate, or mixtures may be resolved by conventional mehtods, eg., chromatography (chromatography with a chiral adsorbens or eluent), or use of a solving agent.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

As described above, the compounds of formula (I) or pharmaceutically acceptable salts thereof can be used as medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB1 receptors.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors, which method comprises administering a compound as defined above to a human being or animal.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors. Such medicaments comprise a compound as defined above.

In this context, the expression 'diseases associated with modulation of CB1 receptors' means diseases which can be treated and/or prevented by modulation of CB1 receptors. Such diseases encompass, but are not limited to, psychic disorders, especially anxiety, psychosis, schizophrenia, depression, abuse of psychotropes, for example for the abuse and/or dependence of a substances, including alcohole dependency and nicotine dependency, neuropathies, migraine, stress, epilepsy, dyskinesias, Parkinson's disease, amnesia, cognitive disorders, senile dementia, Alzheimer's disease, eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), gastrointestinal diseases, vomiting, diarrhea, urinary disorders, cardiovascular disorders, infertility disorders, inflammations, infections, cancer, neuroinflammation, in particular in atherosclerosis, or the Guillain-Barré syndrome, viral encephalitis, cerebral vascular incidents and cranial trauma.

In a preferable aspect, the expression 'diseases associated with modulation of CB1 receptors' relates to eating disorders, obesity, diabetes type II or non insulin dependent diabetes (NIDD), neuroinflammation, diarrhea, abuse and/or dependence of a substances, including alcohole dependency and nicotine dependency. In a more preferable aspect, the said term related to eating disorders, obesity, diabetes type II or non insulin dependent

diabetes (NIDD), abuse and/or dependence of a substances, including alcohole dependency and nicotine dependency, with obesity being especially preferred.

The following tests were carried out in order to determine the activity of the compounds of formula (I).

The affinity of the compounds of the invention for cannabinoid CB1 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB1 receptor is transiently transfected using the Semliki Forest Virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The affinity of the compounds of the invention for cannabinoid CB2 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB2 receptor is transiently transfected using the Semliki Forest virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB1 receptors are stably expressed (see M. Rinaldi-Carmona et. al., J. Pharmacol. Exp. Ther. 278 (1996) 871). The stable expression of the human cannabinoid receptor in cell systems was first described in Nature 1990, 346, 561-564 (CB1) and Nature 1993, 365, 61-65 (CB2) respectively. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB1 receptors by CB1 receptor agonists (e.g. CP-55,940 or (R)-WIN-55212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration dependent manner. This CB1 receptor mediated response can be antagonised by CB1 receptor antagonists such as the compounds of the invention.

The compounds of formula (I) show an excellent affinity for the CB1 receptor, determined with the experimental conditions described in Devane et.al. Mol. Pharmacol. 34 (1988) 605-613. The compounds of the present invention or the pharmaceutically acceptable salts or sovates are antagonists and selective for the CB1 receptor with affinites below IC_{50} = 2 μM. They exhibit at least a 10 fold selectivity against the CB2 receptor.

Compound of Example	IC_{50} [μM]
39	< 2 μM
46	< 2 μM
18	< 2 μM
65	< 2 μM
4	< 2 μM
20	< 2 μM
22	< 2 μM
75	< 2 μM

The compounds of formula (I) and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic

acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 1-100 mg, of a compound of formula (I).

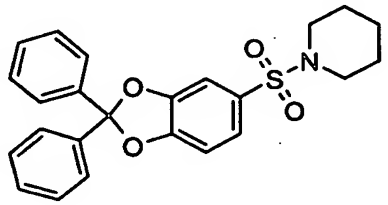
The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

MS = mass spectrometry, ISP = ion spray (positive ion), m.p. = melting point, aq. = aqueous, DMSO = dimethylsulfoxide, NMR = nuclear magnetic resonance spectroscopy, EDCI = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, HPLC = high performance liquid chromatography.

Example 1

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine



2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl chloride (3.36 g, 9 mmol) was dissolved in methylen chloride (135 ml). Piperidine (1.33 ml, 13.5 mmol) and ethyldiisopropyl amine (2.3 ml, 13.5 mmol) were added at room temperature. The reaction was stirred at room temperature over night and washed two times with 1N aqueous HCl solution, twice with 1N aqueous NaOH solution and once with brine. The organic layer was dried over sodium sulfate and filtered. The solvent was evaporated and the residue was purified by column chromatography (4/1 hexane/ethyl acetate eluant). The product was suspended in diethyl ether and filtered to yield a white crystalline solid (1.98 g, 52 %). m.p.: 163-164°C.

Preparation of 2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl chloride:

The sulfonyl chloride derivative was prepared according to literature procedures (WO9218490, EP544166).

Method A

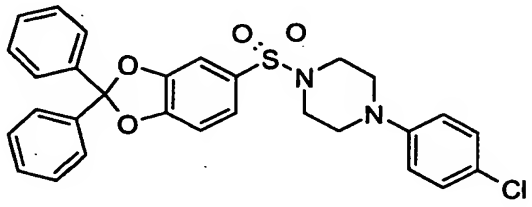
Method A is a general method for the preparation of 2,2-diphenyl-benzo[1,3]dioxole-5-sulfonamides starting from commercially available amines:

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl chloride (93 mg, 0.25 mmol) was dissolved in pyridine (1 ml). The appropriate amine (0.25 mmol) was added and the reaction was heated to 60°C over night. Water was added and solids respectively oils separated. The aqueous phase was decanted and the residue was stirred with acetonitrile. A solid precipitated, which were filtered off and washed with little acetonitrile to yield after drying at high vacuum the product.

The following examples were prepared using the general method A:

Example 2

Preparation of 1-(4-Chloro-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine

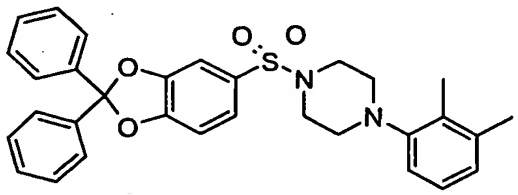


Using 4-(4-chlorophenyl)piperazine (49.2 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (27 mg, 20 %).

MS (ISP): 533.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.44-7.56 (m, 10H), 7.41 (s, 1H), 7.37 (d, 1H), 7.32 (d, 1H), 7.26 (d, 2H), 6.90 (d, 2 H), 3.16-3.19 (m, 4H), 2.98-3.02 (m, 4H).

Example 3

Preparation of 1-(2,3-Dimethyl-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine

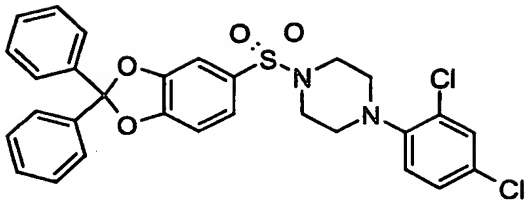


Using 4-(2,3-dimethylphenyl)piperazine hydrochloride (56.7 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (8 mg, 6%).

MS (ISP): 527.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.45-7.60 (m, 5H), 7.47-7.55 (m, 5H), 7.46 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 7.01 (t, 1H), 6.89 (m, 2 H), 3.00-3.12 (m, 4H), 2.82-2.88 (m, 4H), 2.17 (s, 3H), 2.02 (s, 3H).

Example 4

Preparation of 1-(2,4-Dichloro-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine

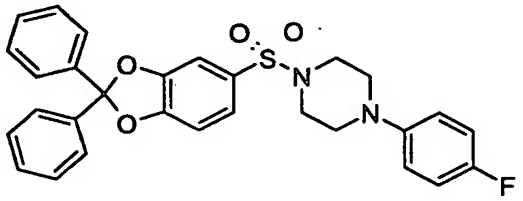


Using 4-(2,4-dichlorophenyl)piperazine hydrochloride (66.9 mg, 0.25 mmol) as an amine, the title compound was obtained as a yellow solid (32 mg, 23%).

MS (ISP): 567.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.45-7.60 (m, 10H), 7.42 (s, 1H), 7.34-7.39 (m, 4H), 7.31 (d, 1H), 7.16 (d, 1H), 3.00–3.08 (m, 8H).

Example 5

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-piperazine

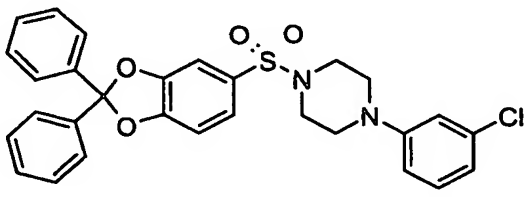


Using 4-(4-fluorophenyl)piperazine (45.1 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (66.4 mg 51 %).

MS (ISP): 517.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.51-7.56 (m, 4H), 7.45-7.49 (m, 6H), 7.41 (s, 1H), 7.37 (d, 1H), 7.29 (d, 1H), 7.02 (t, 1H), 6.90-6.94 (m, 1H), 3.11 (m, 4H), 3.01 (m, 4H).

Example 6

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(3-chloro-phenyl)-piperazine

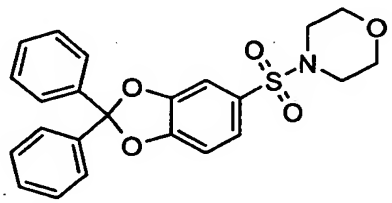


Using 4-(3-chlorophenyl)piperazine (49.2 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (91.4 mg, 68 %).

MS (ISP): 533.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.48-7.56 (m, 4H), 7.44-7.48 (m, 6H), 7.41 (s, 1H), 7.36 (d, 1H), 7.29 (d, 1H), 7.19 (t, 1H), 6.91 (s, 1H), 6.82 (d, 1H), 6.79 (d, 1H), 3.23 (m, 4H), 3.00 (m, 4H).

Example 7

Preparation of 4-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-morpholine

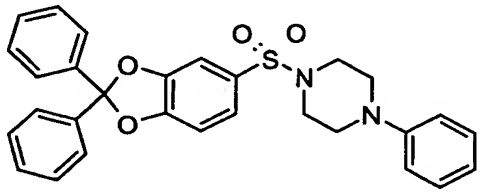


Using morpholine (21.8 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (51.1 mg 48 %).

MS (ISP): 424.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.57 (m, 4H), 7.46-7.49 (m, 6H), 7.37 (s, 1H), 7.33 (d, 1H), 7.29 (d, 1H), 3.61 (m, 4H), 2.86 (m, 4H).

Example 8

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-phenyl-piperazine

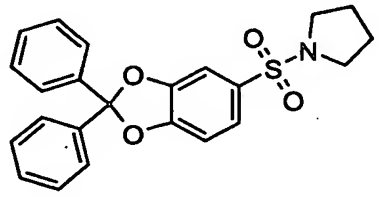


Using 4-phenylpiperazine (40.6 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (78.7 mg, 63 %).

MS (ISP): 499.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.56 (m, 4H), 7.44-7.48 (m, 6H), 7.41 (s, 1H), 7.35 (d, 1H), 7.30 (d, 1H), 7.19 (t, 2H), 6.89 (d, 2H), 6.77 (t, 1H), 3.17 (m, 4H), 3.02 (m, 4H).

Example 9

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-pyrrolidine

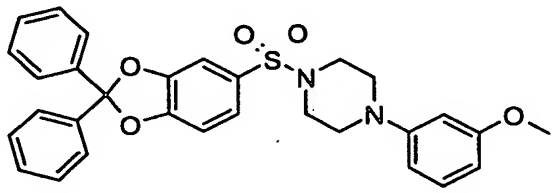


Using pyrrolidine (17.8 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (67.8 mg, 67 %).

MS (ISP): 408.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.53-7.57 (m, 4H), 7.43-7.49 (m, 7H), 7.39 (d, 1H), 7.25(d, 1H), 3.12 (m, 4H), 1.64 (m, 4H).

Example 10

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(3-methoxy-phenyl)-piperazine

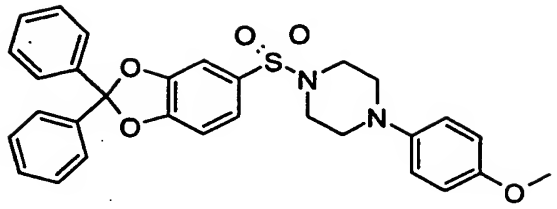


Using 4-(3-methoxyphenyl)piperazine dihydrochloride (66.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (75.9 mg, 58 %).

MS (ISP): 529.3 ($M+H^+$,100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.56 (m, 4H), 7.44-7.48 (m, 6H), 7.41 (s, 1H), 7.37 (d, 1H), 7.29 (d, 1H), 7.08 (t, 1H), 6.48 (d, 1H), 6.42 (s, 1H), 6.38 (d, 1H), 3.68 (s, 3H), 3.17 (m, 4H), 3.01 (m, 4H).

Example 11

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-methoxy-phenyl)-piperazine

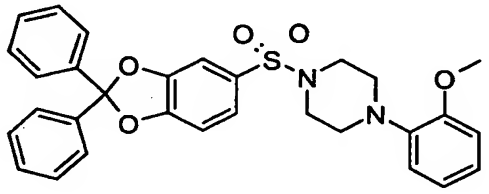


Using 4-(4-methoxyphenyl)piperazine dihydrochloride (66.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a light brown solid (78.9 mg, 60 %).

MS (ISP): 529.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.57 (m, 4H), 7.45-7.48 (m, 6H), 7.38 (s, 1H), 7.36 (d, 1H), 7.31 (d, 1H), 6.85 (d, 2H), 6.78 (d, 2H), 3.66 (s, 3H), 3.03 (m, 8H).

Example 12

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-methoxy-phenyl)-piperazine

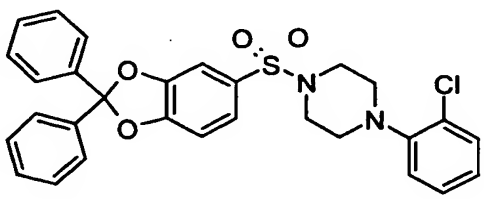


Using 4-(2-methoxyphenyl)piperazine (48.1 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (66.3 mg, 50 %).

MS (ISP): 529.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.54-7.58 (m, 4H), 7.45-7.49 (m, 6H), 7.41 (s, 1H), 7.38 (d, 1H), 7.31 (d, 1H), 6.85-6.94 (m, 4H), 3.70 (s, 3H), 3.01 (m, 8H).

Example 13

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-chloro-phenyl)-piperazine

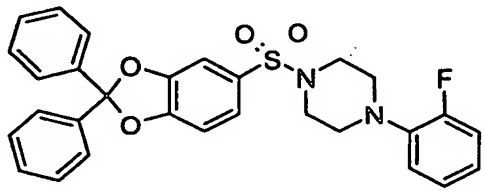


Using 4-(2-chlorophenyl)piperazine hydrochloride (58.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (80.4 mg, 60 %).

MS (ISP): 533.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.54-7.58 (m, 4H), 7.45-7.49 (m, 7H), 7.43 (s, 1H), 7.38 (d, 1H), 7.32 (d, 1H), 7.30 (t, 1H), 7.15 (d, 1H), 7.06 (t, 1H), 3.04 (m, 8H).

Example 14

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-fluoro-phenyl)-piperazine

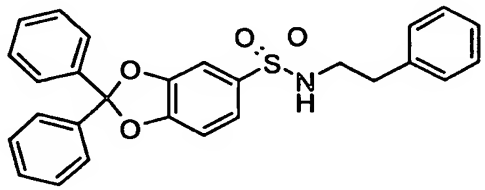


Using 4-(2-fluoroophenyl)piperazine (45.1 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (92.8 mg 72 %).

MS (ISP): 517.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.54-7.57 (m, 4H), 7.45-7.49 (m, 6H), 7.42 (s, 1H), 7.37 (d, 1H), 7.31 (d, 1H), 6.96-7.17 (m, 4H), 3.05 (m, 8H).

Example 15

Preparation of 2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid phenethyl-amide

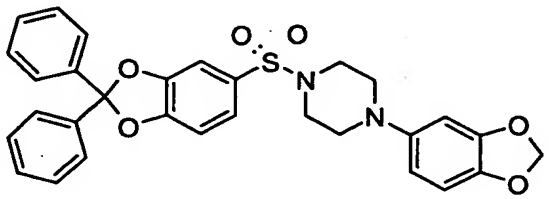


Using phenylethylamine (30.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (46.0 mg, 40 %).

MS (ISP): 458.4 ($M+H^+$, 100), 475.3 ($M+NH_4^+$, 45). NMR (300 MHz, DMSO-d_6) ppm: 7.44-7.56 (m, 11H), 7.33-7.21 (m, 2H), 7.10-7.21 (m, 6H), 2.95 (q, 2H), 2.64 (t, 2H).

Example 16

Preparation of 1-Benzo[1,3]dioxol-5-yl-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine

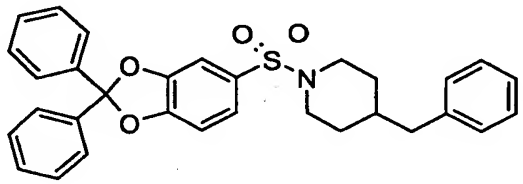


Using 4-(3,4-dioxymethylenephenyl)piperazine hydrochloride (64.7 mg, 0.25 mmol) as an amine, the title compound was obtained as a brown solid (46.6 mg, 42 %).

MS (ISP): 543.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.42-7.56 (m, 10H), 7.41 (s, 1H), 7.36 (d, 1H), 7.29 (d, 1H), 6.74 (d, 1H), 6.63 (s, 1H), 6.30 (d, 1H), 5.90 (s, 2H), 3.02 (m, 8H).

Example 17

Preparation of 4-Benzyl-1-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine



Using 4-benzylpiperidine (43.8 mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (37.6 mg, 29 %).

MS (ISP): 512.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.56 (m, 4H), 7.45-7.48 (m, 6H), 7.08-7.32 (m, 8H), 3.58 (m, 2H), 2.45 (m, 2H), 2.19 (m, 2H), 1.58 (m, 3H), 1.15 (m, 1H).

Method B

Method B is a general method for the preparation of 2,2-diphenyl-benzo[1,3]dioxole-5-sulfonamides starting from commercially available amines:

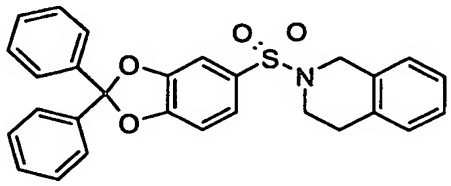
2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl chloride (93 mg, 0.25 mmol) was dissolved in pyridine (1 ml). The appropriate amine (0.25 mmol) was added and the reaction was heated to 60°C over night. Water was added and solids respectively oils separated. The

aqueous phase was decanted and the residue was stirred with acetonitrile. A solution was obtained, which was subjected to preparative reversed phase chromatography (gradient of acetonitrile/water containing 0.1 % formic acid as the eluent) to yield after evaporation of the eluant and drying the product.

The following examples were prepared using the general method B:

Example 18

Preparation of 2-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline

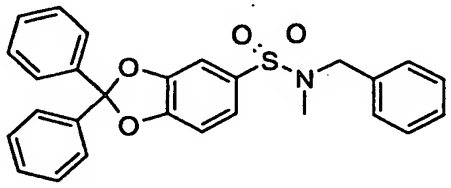


Using 1,2,3,4-tetrahydro-isoquinoline (33.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a yellow solid (35 mg, 30 %).

MS (ISP): 470.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.40-7.54 (m, 12H), 7.24 (d, 1H), 7.05-7.13 (m, 4 H), 4.19 (s, 2H), 3.30 (t, 2H), 2.82 (m, 2H).

Example 19

Preparation of 2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid benzyl-methyl-amide

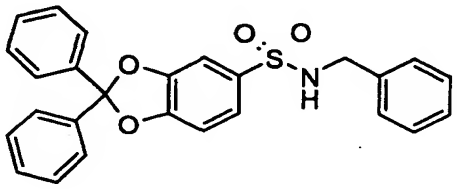


Using N-methylbenzylamine (30.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a yellow solid (48.3 mg, 42 %).

MS (ISP): 458.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.43-7.58 (m, 12H), 7.27-7.33 (m, 6H), 4.13 (s, 2H), 2.53 (s, 3H).

Example 20

Preparation of 2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid benzylamide

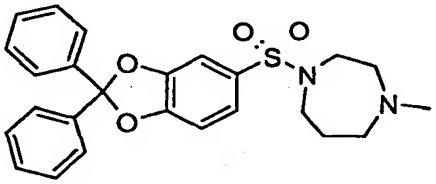


Using benzylamine (26.8 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (25.1 mg, 22 %).

MS (ISN): 442.2 ($M-H^+$, 100), 502.1 ($M+OAc^-$, 20). NMR (300 MHz, DMSO-d_6) ppm: 8.06 (t, 1H, NH), 7.46-7.56 (m, 11H), 7.36 (d, 1H), 7.32 (s, 1H), 7.14-7.18 (m, 5H), 3.97 (d, 2H).

Example 21

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-methyl-[1,4]diazepane

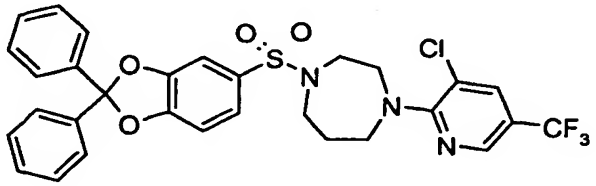


Using N-methylhomopiperazine (28.5 mg, 0.25 mmol) as an amine, the title compound was obtained as a light brown solid (23.6 mg, 21 %).

MS (ISP): 451.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.45-7.56 (m, 10H), 7.41 (s, 1H), 7.36 (d, 1H), 7.23 (s, 1H), 3.22-3.39 (m, 4H), 2.50 (m, 4H, under the DMSO peak), 2.20 (s, 3H), 1.68-1.74 (m, 2H).

Example 22

Preparation of 1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-[1,4]diazepane

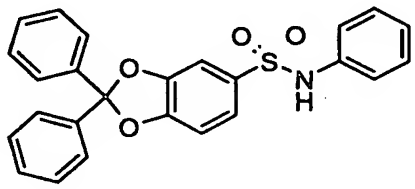


Using 1-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-homopiperazine (69.8 mg, 0.25 mmol) as an amine, the title compound was obtained as a yellow solid (76.9 mg, 52 %).

MS (ISP): 616.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 8.38 (s, 1H), 7.95 (s, 1H), 7.44-7.55 (m, 10H), 7.41 (s, 1H), 7.33 (d, 1H), 7.15 (s, 1H), 3.84 (t, 2H), 3.76 (t, 2H), 3.44 (t, 2H), 3.28 (t, 2H), 1.89 (m, 2H).

Example 23

Preparation of 2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid phenylamide

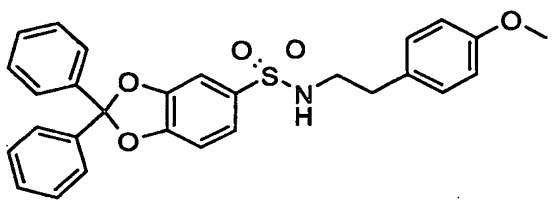


Using aniline (23.3 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (18.2 mg, 17 %).

MS (ISN): 428.3 ($M-H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 10.19 (s, 1H, NH), 7.43-7.52 (m, 10H), 7.32-7.35 (m, 2H), 7.14-7.21 (m, 3H), 6.98-7.09 (m, 3H).

Example 24

Preparation of 2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid [2-(4-methoxy-phenyl)-ethyl]-amide

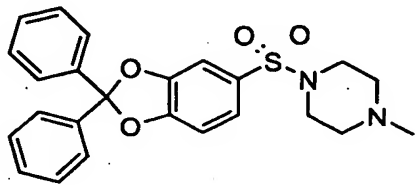


Using 2-(4-methoxyphenyl)ethylamine (37.8 mg, 0.25 mmol) as an amine, the title compound was obtained as a light yellow solid (67.1 mg, 55 %).

MS (ISN): 486.2 ($M-H^+$, 100), 546.1 ($M+OAc^-$, 35). NMR (300 MHz, DMSO-d_6) ppm: 7.44-7.58 (m, 11H), 7.34-7.37 (m, 2H), 7.19 (d, 1H), 7.03 (d, 2H), 6.79 (d, 2H), 3.69 (s, 3H), 2.89 (q, 2H), 2.58 (t, 2H).

Example 25

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-methyl-piperazine

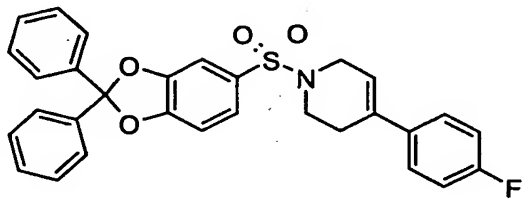


Using N-methylpiperazine (25.0mg, 0.25 mmol) as an amine, the title compound was obtained as a white solid (11 mg, 10 %).

MS (ISP): 437.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.53-7.57 (m, 4H), 7.45-7.49 (m, 6H), 7.36 (s, 1H), 7.32 (d, 1H), 7.29 (d, 1H), 2.87 (m, 4H), 2.33 (m, 4H), 2.11 (s, 3H).

Example 26

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine

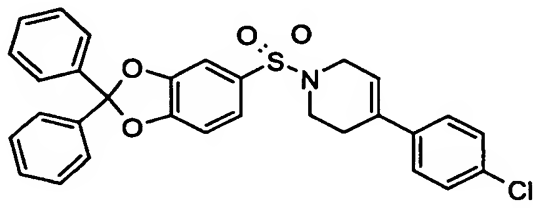


4-(4-Fluorophenyl)-1,2,3,4-tetrahydropyridin hydrochloride (2.56 g, 12 mmol) was suspended in methylene chloride (150 ml). Ethyldiisopropylamine (4.2 ml, 25 mmol) was added and the solution was stirred for 10 minutes at room temperature. 2,2-Diphenyl-benzo[1,3]dioxole-5- sulfonyl chloride (3.72 g, 10 mmol) was added and the reaction was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by column chromatography on silical gel (100 g, CH_2Cl_2 eluant). The product was stirred with n-hexane, filtered and dried to yield the sulfonamide as white crystals (3.86 g, 75 %).

MS (ISP): 514.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.50-7.54 (m, 4H), 7.44-7.48 (m, 7H), 7.36-7.40 (m, 3H), 7.26 (d, 1H), 7.09 (t, 2H), 6.03 (m, 1H), 3.68 (m, 2H), 3.23 (t, 2H), 2.50 (s, 2H, under DMSO peak).

Example 27

Preparation of 4-(4-Chloro-phenyl)-1-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-1,2,3,6-tetrahydro-pyridine

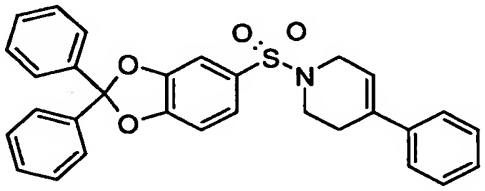


4-(4-Chlorophenyl)-1,2,3,4-tetrahydropyridin hydrochloride (19.37 mg, 0.10 mmol) was suspended in methylene chloride (2 ml). Ethyldiisopropylamine (0.035 ml, 0.20 mmol) was added and the solution was shaken for 10 minutes at room temperature. 2,2-Diphenyl-benzo[1,3]dioxole-5- sulfonyl chloride (37.28 mg, 0.10 mmol) was added and the reaction was shaken at room temperature for 12 hours. Aqueous HCl (0.1 N, 1.0 ml) was added and the mixture shaken for 30 minutes, the aqueous layer removed and the organic phase concentrated and purified by preparative reverse phase HPLC (YMC, ODS-AQ packing; 20%→95% CH_3CN/H_2O) to yield the sulfonamide (2.6 mg, 5 %).

MS (ISP): 530.2 ($M+H^+$, 100). NMR (500 MHz, DMSO-d_6) ppm: 7.31-7.56 (m, 16H), 7.26 (d, 1H), 6.10 (m, 1H), 3.70 (m, 2H), 3.24 (m, 2H), 2.50 (m, 2H, under DMSO peak).

Example 28

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-phenyl-1,2,3,6-tetrahydro-pyridine



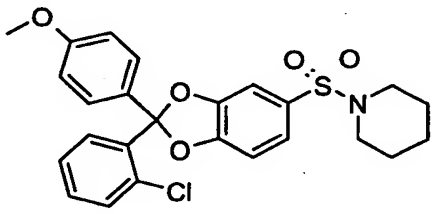
4-Phenyl-1,2,3,4-tetrahydropyridin hydrochloride (15.92 mg, 0.10 mmol) was suspended in methylene chloride (2 ml). Ethyldiisopropylamine (0.035 ml, 0.20 mmol) was added and the solution was shaken for 10 minutes at room temperature. 2,2-Diphenyl-benzo[1,3]dioxole-5- sulfonyl chloride (37.28 mg, 0.10 mmol) was added and the reaction was shaken at room temperature for 12 hours. Aqueous HCl (0.1 N, 1.0 ml) was added and the mixture shaken for 30 minutes, the aqueous layer removed and the organic phase

concentrated and purified by preparative reverse phase HPLC (YMC, ODS-AQ packing; 20%→95% CH_3CN/H_2O) to yield the sulfonamide (23.6 mg, 48 %).

MS (ISP): 596.2 ($M+H^+$, 100). NMR (500 MHz, DMSO-d_6) ppm: 7.22-7.55 (m, 17H), 6.06 (m, 1H), 3.70 (m, 2H), 3.24 (m, 2H), 2.50 (m, 2H, under DMSO peak).

Example 29

Preparation of racemic 1-[2-(2-Chloro-phenyl)-2-(4-methoxy-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine



Method C

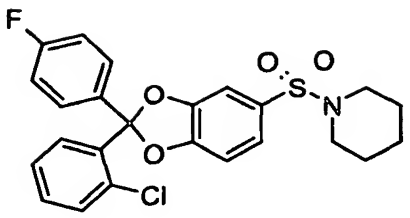
4-(Piperidine-1-sulfonyl)-benzene-1,2-diol (60 mg, 0.2 mmol) and (4-methoxyphenyl)-(2-chlorophenyl)-dichloromethane (51 mg, 0.2 mmol) was refluxed over night in toluene (2 ml). After cooling the reaction to room temperature the solvent was evaporated. The residue was dissolved in methylene chloride and purified by column chromatography (methylene chloride eluant) on silica gel to afford the product as a colorless solid (42 mg, 39 %).

MS (ISP): 486.3 ($M+H^+$, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.80-7.90 (m, 1H), 7.30-7.43 (m, 8H), 6.97 (d, 1H), 6.89 (d, 1H), 3.82 (s, 3H), 2.98 (m, 4H), 1.60-1.70 (m, 4H), 1.40-1.50 (m, 2H).

The following examples were prepared following method C:

Example 30

Preparation of racemic 1-[2-(2-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine

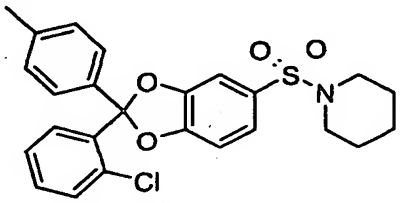


Using 4-fluorophenyl-2-chlorophenyl-dichloromethane (57 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless foam (68 mg, 71 %). Column chromatography was performed on silica gel (25 g, methylene chloride eluant).

MS (ISP): 474.2 ($M+H^+$, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.84 (m, 1H), 7.32-7.47 (m, 6H), 7.27 (d, 1H), 7.08 (t, 2H), 6.99 (d, 1H), 2.95-3.01 (m, 4H), 1.60-1.68 (m, 4H), 1.42-1.47 (m, 2H).

Example 31

Preparation of racemic 1-[2-(2-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine

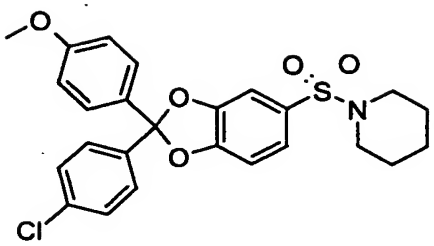


Using 4-methylphenyl-2-chlorophenyl-dichloromethane (57 mg, 0.2 mmol) as a starting material, the title compound was obtained as a light yellow foam (46 mg, 44 %). Column chromatography was performed on silica gel (25 g, methylene chloride eluant).

MS (ISP): 470.2 ($M+H^+$, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.83 (m, 1H), 7.31-7.42 (m, 7H), 7.20 (d, 2H), 6.97 (d, 1H), 2.96-3.02 (m, 4H), 1.60-1.68 (m, 4H), 1.42-1.46 (m, 2H).

Example 32

Preparation of racemic 1-[2-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine

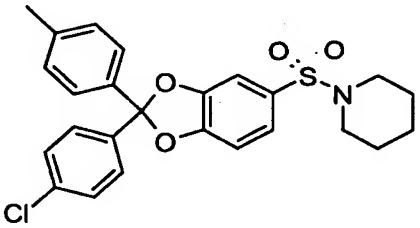


Using 4-Methoxphenyl-4-chlorophenyl-dichloromethane (60 mg, 0.2 mmol) as a starting material, the title compound was obtained as a light red solid (35 mg, 36 %). Column chromatography was performed on silica gel (25 g, methylene chloride eluant).

MS (EI): 485.2 (M^+, 65), 374.2 ($[M-PhCl]^+$, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.49 (d, 2H), 7.42 (d, 2H), 7.32 (d, 2H), 7.22 (s, 1H), 6.94 (d, 1H), 6.90 (d, 2H), 2.95-2.99 (m, 4H), 1.60-1.68 (m, 4H), 1.40-1.44 (m, 2H).

Example 33

Preparation of racemic 1-[2-(4-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine

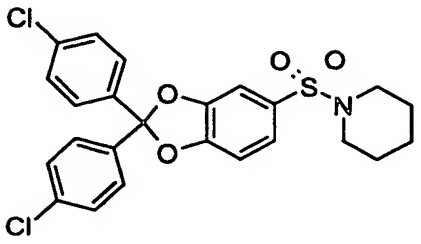


Using 4-Methylphenyl-4-chlorophenyl-dichloromethane (85 mg, 0.3 mmol) as a starting material, the title compound was obtained as a colorless foam (138 mg, 97 %). Column chromatography was performed on silica gel (25 g, 4/1 hexane/ethyl acetate eluant).

MS (ISP): 470.2 (M^+, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.49 (d, 2H), 7.40 (d, 2H), 7.36 (d, 2H), 7.31 (d, 1H), 7.23 (d, 1H), 6.94 (d, 2H), 2.95-2.99 (m, 4H), 1.60-1.68 (m, 4H), 1.39-1.46 (m, 2H).

Example 34

Preparation of 1-[2,2-Bis-(4-chloro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine

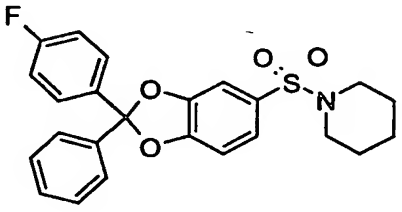


Using bis-(4-chlorophenyl)-dichloromethane (61 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless solid (77 mg, 78 %). Column chromatography was performed on silica gel (25 g, methylene chloride eluant).

MS (EI): 489.1 (M^+, 30), 378.1 ([M-PhCl] $^+$, 30), 231.1 (70), 84.3 (100). NMR (300 MHz, $CDCl_3$) ppm: 7.47 (d, 4H), 7.37 (d, 4H), 7.33 (d, 1H), 7.25 (s, 1H), 6.96 (d, 1H), 2.95-3.00 (m, 4H), 1.60-1.68 (m, 4H), 1.40-1.46 (m, 2H).

Example 35

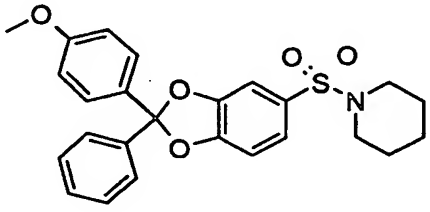
Preparation of racemic 1-[2-(4-Fluoro-phenyl)-2-phenyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine



Using 4-fluorophenyl-phenyl-dichloromethane (51 mg, 0.2 mmol) as a starting material, the title compound was obtained as a white crystalline solid (66 mg, 75 %) after stirring the crude product in diethyl ether (time?), filtration and drying. m.p.: 125-126°C.

Example 36

Preparation of racemic 1-[2-(4-Methoxy-phenyl)-2-phenyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine

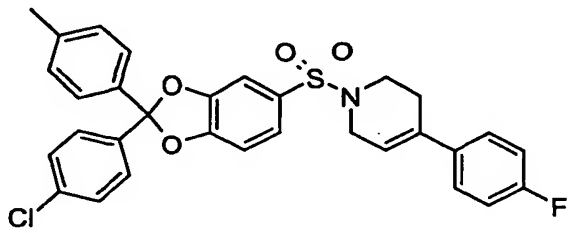


Using 4-methoxyphenyl-phenyl-dichloromethane (53 mg, 0.2 mmol) as a starting material, the title compound was obtained as a white solid (56 mg, 62 %). Column chromatography was performed on silica gel (25 g, 4/1hexane/ethyl acetate).

MS (ISP): 452.4 (M^+, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.41-7.54 (m, 7H), 7.33 (s, 1H), 7.31 (d, 4H), 7.23 (d, 1H), 7.00 (d, 2H), 3.76 (s, 3H), 2.87 (m, 4H), 1.53 (m, 4H), 1.35 (m, 2H).

Example 37

Preparation of racemic 1-[2-(4-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine



Using 4-Chlorophenyl-4-methylphenyl-dichloromethane (57 mg, 0.2 mmol) and 4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-sulfonyl]-benzene-1,2-diol (69 mg, 0.2 mmol) as a starting material, the title compound was obtained as an off-white crystalline solid (90 mg, 80 %) after taking the residue up in hexane/ethyl acetate (4/1), stirring for 10 minutes, filtering the solid off and drying.

MS (EI): 561.2 (M^+, 10), 176.2 (100), 149.2 (50). NMR (300 MHz, $CDCl_3$) ppm: 7.47 (d, 2H), 7.18-7.40 (m, 9H), 6.99 (d, 2H), 6.96 (d, 2H), 5.89 (m, 1H), 3.75 (m, 2H), 3.32 (t, 2H), 2.57 (m, 2H), 2.36 (s, 3H).

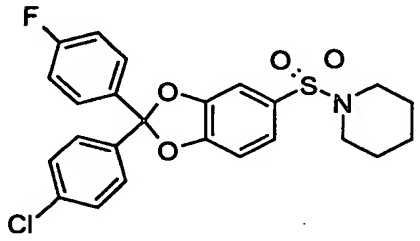
Preparation of 4-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridine-1-sulfonyl]-benzene-1,2-diol

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine (3.2 g, 6.2 mmol) was dissolved in methylene chloride (100 ml). Trifluoroacetic acid (50 ml) was added dropwise and the reaction was stirred for 5 hours at room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel (100 g, methylene chloride then ethyl acetate as eluant). The product was crystallized from ether/hexane to give a white solid (2.1 g, 96%).

MS (ISN): 348.2 ($M-H^+$, 100). NMR (300 MHz, , DMSO-d_6) ppm: 10.0 (br s, 1H, OH), 9.80 (br s, 1H, OH), 7.44 (d, 1H), 7.42 (d, 1H), 7.08-7.19 (m, 4H), 6.92 (d, 1H), 6.07 (brs, 1H), 3.59 (br s, 2H), 3.13 (m, 2H), 2.51 (m, 2H, under DMSO peak).

Example 38

Preparation of racemic 1-[2-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine

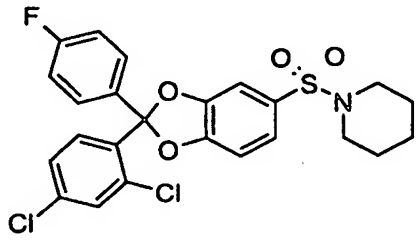


Using 4-chlorophenyl-4-fluorophenyl-dichloromethane (57 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless foam (77 mg, 81 %). Column chromatography was performed on silica gel (25 g, 4/1 hexane/ethyl acetate eluant).

MS (EI): 473.2 (M^+, 30), 215.2 (40), 84.3 (100). NMR (300 MHz, $CDCl_3$) ppm: 7.46-7.53 (m, 4H), 7.32-7.39 (m, 3H), 7.24 (s, 1H), 7.09 (t, 2H), 6.96 (d, 1H), 2.96-3.00 (m, 4H), 1.60-1.68 (m, 4H), 1.40-1.46 (m, 2H).

Example 39

Preparation of racemic 1-[2-(2,4-Dichloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine



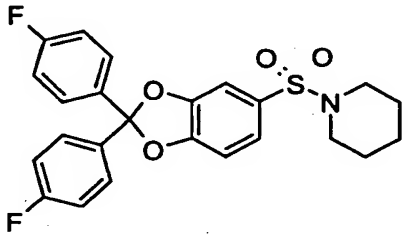
Using 2,4-dichlorophenyl-4-fluorophenyl-dichloromethane (65 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless foam (81 mg, 80 %).

Column chromatography was performed on silica gel (25 g, 4/1 hexane/ethyl acetate eluant).

MS (ISP): 508.2 ($M+H^+$, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.78 (d, 1H), 7.32-7.47 (m, 3H), 7.32-7.37 (m, 2H), 7.28 (s, 1H), 7.08 (t, 2H), 6.99 (d, 1H), 2.97-3.00 (m, 4H), 1.61-1.68 (m, 4H), 1.40-1.47 (m, 2H).

Example 40

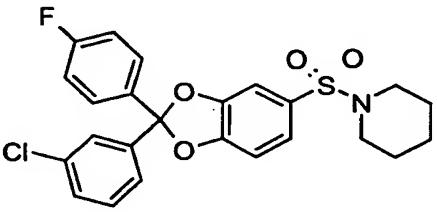
Preparation of 1-[2,2-Bis-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine



Using bis-(4-fluorophenyl)-dichloromethane (55 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless foam (75 mg, 82 %). Column chromatography was performed on silica gel (25 g, 4/1 hexane/ethyl acetate eluant). m.p.: 148 – 149°C.

Example 41

Preparation of racemic 1-[2-(3-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine

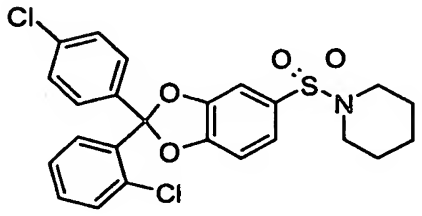


Using 3-chlorophenyl-4-fluorphenyl-dichloromethane (58 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless viscous oil (82 mg, 86 %). Column chromatography was performed on silica gel (25 g, 4/1 hexane/ethyl acetate eluant).

MS (ISP): 474.2 ($M+H^+$, 100). NMR (300 MHz, $CDCl_3$) ppm: 7.49-7.55 (m, 3H), 7.33-7.44 (m, 4H), 7.26 (s, 1H), 7.09 (t, 2H), 6.97 (d, 1H), 2.96-3.00 (m, 4H), 1.60-1.68 (m, 4H), 1.40-1.46 (m, 2H).

Example 42

Preparation of racemic 1-[2-(4-Chloro-phenyl)-2-(2-chloro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine



Using 2-chlorophenyl-4-chlorophenyl-dichloromethane (61 mg, 0.2 mmol) as a starting material, the title compound was obtained as a colorless solid (40 mg, 41 %). Column chromatography was performed on silica gel (25 g, CH_2Cl_2 eluant).

MS (EI): 489.1 (M^+, 30), 378.1 (35), 231.1 (60), 84.2 (100). NMR (300 MHz, $CDCl_3$) ppm: 7.42-7.86 (m, 1H), 7.33-7.44 (m, 8H), 7.27 (d, 1H), 6.99 (d, 1H), 2.96-3.00 (m, 4H), 1.60-1.68 (m, 4H), 1.42-1.47 (m, 2H).

Method D

The bisaryl-dichloromethane derivatives needed for the preparation of the above described examples were prepared according to the following method D following a literature procedure (R. K. Ramchandani, R. D. Wakharkar, A. Sudalai, Tetrahedron Lett. 37 (23) (1996) 4063-4064).

Preparation of (4-methoxyphenyl)(2-chlorophenyl)-dichloromethane:

Aluminium trichloride (400 mg, 3 mmol) is suspended in 1,2-dichlorethane (1.4 ml). At 0°C under argon 2-chlorobenzotrifluoride (180 mg, 1 mmol) is added. A deep red solution is obtained to which anisol (108 mg, 1 mmol) is added. The reaction was stirred at 0°C for 3 hours. It was poured onto ice, stirred for 5 minutes and extracted twice with methylene chloride. The combined organic layers were washed with brine, dried over sodium sulfate and filtered. The solvent was evaporated to leave the product as dark red viscous oil (416 mg 138 %), which was used without purification in the next step.

Known bisaryl-dichlormethanes prepared by this method:

4-Methylphenyl-4-chlorophenyl-dichloromethane

Bis-(4-chlorophenyl)-dichloromethane

2-Chlorophenyl-4-chlorophenyl-dichloromethane

(4-Methoxyphenyl)(2-chlorophenyl)-dichloromethane

The following bisaryl-dichlormethane derivatives are unknown in literature and are prepared according to method D from commercially available starting materials. The compounds were not purified, because some of them are instable on column chromatography, but were used instead without purification as crude products in the next step:

Preparation of 4-fluorophenyl-2-chlorophenyl-dichloromethane:

From 2-chlorobenzotrifluorid (180 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and fluorobenzol (96 mg, 1 mmol), light yellow oil (380 mg, 131 % crude).

Preparation of 4-methylphenyl-2-chlorophenyl-dichloromethane:

From 2-chlorobenzotrifluorid (180 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and toluene (92 mg, 1 mmol), light yellow oil (345 mg, 120 % crude).

Preparation of 4-methoxyphenyl-4-chlorophenyl-dichloromethane:

From 4-chlorobenzotrifluorid (180 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and anisol (108 mg, 1 mmol), red solid (345 mg, 120 % crude), contains the benzophenone (ca 30 %).

Preparation of 4-chlorophenyl-4-fluorophenyl-dichloromethane:

From 4-chlorobenzotrifluorid (180 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and fluorobenzene (96 mg, 1 mmol), light yellow oil (382 mg, 131 % crude).

Preparation of 2,4-dichlorophenyl-4-fluorophenyl-dichloromethane:

From 2,4-dichlorobenzotrifluorid (215 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and fluorobenzene (96 mg, 1 mmol), light yellow oil (382 mg, 118 % crude).

Preparation of 3-chlorophenyl-4-fluorophenyl-dichloromethane:

From 3-chlorobenzotrifluorid (180 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and fluorobenzene (96 mg, 1 mmol), light yellow oil (384 mg, 132 % crude).

Preparation of 4-fluorophenyl-phenyl-dichloromethane:

From benzotrifluorid (146 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and fluorobenzene (96 mg, 1 mmol), light yellow oil (335 mg, 131 % crude).

The following bisaryl-dichloromethanes are known in the literature but their synthesis is not described. These compounds were prepared with method D:

Preparation of bis-(4-fluorophenyl)-dichloromethane (EP96008).

From 4-fluorobenzotrifluorid (164 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and fluorobenzene (96 mg, 1 mmol), light yellow oil (377 mg, 138 % crude).

Preparation of 4-methoxyphenyl-phenyl-dichloromethane (R. Laatikainen, V. Kral, J. Chem. Soc., Perkin Trans. 2 (8) (1985) 1091-1100; US 3824310):

From benzotrifluorid (146 mg, 1 mmol), $AlCl_3$ (400 mg, 3 mmol) and anisol (108 mg, 1 mmol), dark red viscous oil (352 mg, 132 % crude).

Preparation of 4-(Piperidine-1-sulfonyl)-benzene-1,2-diol:

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine (1.92 g, 4.5 mmol) was dissolved in methylene chloride (69 ml). At room temperature trifluoroacetic acid (20.7 ml) and than water (8 drops) were added. The reaction was stirred at room temperature for 24 hours. The solvent was evaporated and the residue was three times taken up in n-pentane and evaporated again in order to remove trifluoroacetic acid. The residue was purified by column chromatography on silica gel (100 g, methylene chloride then 1/19 methanol/methylene chloride eluant). The product was precipitated from diethyl ether/n-pentane. The solvent was evaporated and the residue was stirred with n-pentane. The solid was filtered and dried to yield the product as a white crystalline solid (1.13 g, 97 %).

MS (ISN): 256.0 ($M-H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 9.98(s, 1H, OH), 9.69 (s, 1H, OH), 7.05 (dd, 1H), 7.01 (dd, 1H), 6.90 (d, 1H), 2.78-2.83 (m, 4H), 1.50-1.68 (m, 4H), 1.30-1.40 (m, 2H).

Method E

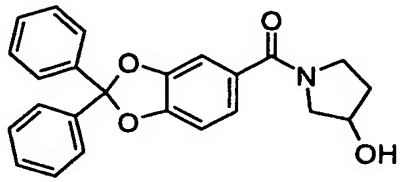
2,2-Diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), the appropriate amine (22 mg, 0.25 mmol) and ethyldiisopropylamine (32 mg, 0.25 mmol) were dissolved in acetonitrile (2 ml) and stirred at room temperature for 3 hours. Water (20 ml) was added and the reaction was stirred at room temperature for 1 hour. The precipitate was filtered off, washed with water and dried at high vacuum to yield the product as a crystalline white solid.

The preparation of the activated ester, 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester, is described in the literature (EP544166).

The following examples were prepared following method E:

Example 43

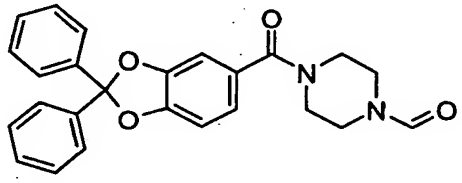
Preparation of racemic (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(3-hydroxy-pyrrolidin-1-yl)-methanone



From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and 3-pyrrolidinol (22 mg, 0.25 mmol), the title compound was obtained as a white crystalline solid (73 mg, 94 %). m.p.: 106-107°C.

Example 44

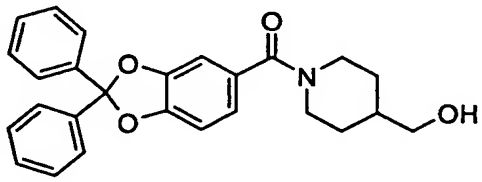
Preparation of 4-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbaldehyde



From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and formyl-piperazine (32 mg, 90 % pure, 0.25 mmol), the title compound was obtained as a white crystalline solid (73 mg, 88 %). m.p. 176-177°C.

Example 45

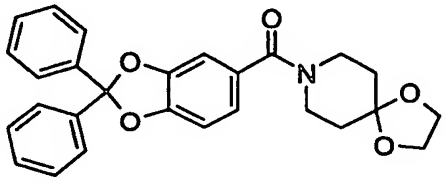
Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-hydroxymethyl-piperidin-1-yl)-methanone



From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and 4-(hydroxymethyl)-piperidine (29 mg, 0.25 mmol), the title compound was obtained as a white crystalline solid (76 mg, 91 %). m.p. 197-198°C.

Example 46

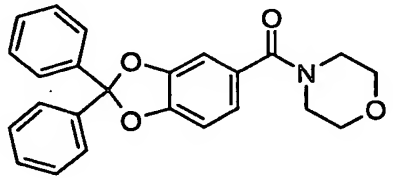
Preparation of (1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone



From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and 1,4-dioxa-8-azaspiro(4,5)decan (36 mg, 0.25 mmol), the title compound was obtained as a white crystalline solid (74 mg, 83 %). m.p. 150-151°C.

Example 47

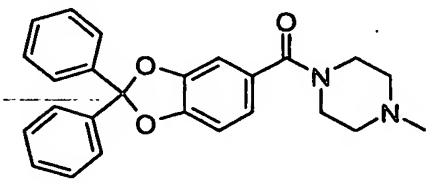
Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone



From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and morpholine (22 mg, 0.25 mmol), the title compound was obtained as a white crystalline solid (64 mg, 82 %). m.p. 149-150°C.

Example 48

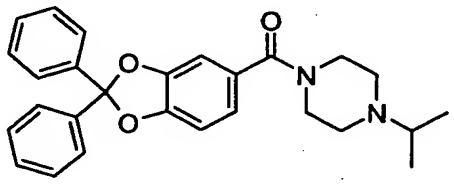
Preparation (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone



From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and 1-methylpiperazine (25 mg, 0.25 mmol), the title compound was obtained as a white crystalline solid (72 mg, 90 %). m.p. 115-116°C.

Example 49

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-isopropyl-piperazin-1-yl)-methanone

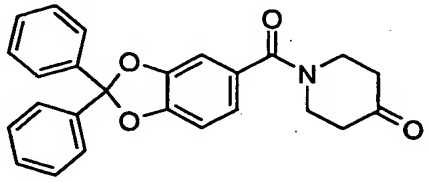


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol) and 1-(2-propyl)-piperazine (32 mg, 0.25 mmol), the title compound was obtained as a colorless foam (84 mg, 98 %). Work up: after addition of water (20 ml), the reaction was stirred for 1 hour at room temperature. Methylene chloride was added and the mixture was stirred for further 10 minutes. The organic layer was separated, washed with water and dried over sodium sulfate. The solvent was evaporated to yield the product after drying at high vacuum.

MS (ISP): 429.6 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.51-7.56 (m, 4H), 7.43-7.47 (m, 6H), 7.08 (d, 1H), 7.07 (s, 1H), 6.92 (d, 1H), 3.3-3.6 (br m, 4H), 2.65 (sept, 1H), 2.38-2.42 (br m, 4H), 0.95 (d, 6H).

Example 50

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidin-4-one



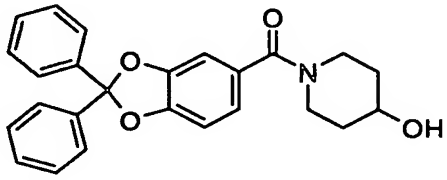
From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 4-piperidon monohydrate hydrochloride (39 mg, 0.25 mmol) and ethyl-diisopropylamine (58 mg, 0.45 mmol), the title compound was obtained as a light yellow foam (75 mg, 94 %). Work up: after addition of water (20 ml), the reaction was stirred for

1 hour at room temperature. Methylene chloride was added and the mixture was stirred for further 10 minutes. The organic layer was separated, washed with water and dried over sodium sulfate. The solvent was evaporated to yield the product after drying at high vacuum.

MS (ISP): 400.5 ($M+H^+$, 100), 417.3 ($M+NH_4^+$, 40), 799.3 ($2M+H^+$, 20). NMR (300 MHz, DMSO-D_6) ppm: 7.47-7.57 (m, 4H), 7.44-7.47 (m, 6H), 7.17 (s, 1H), 7.11 (d, 1H), 7.05 (d, 1H), 3.62-3.82 (br m, 4H), 2.39-2.44 (br m, 4H).

Example 51

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-hydroxy-piperidin-1-yl)-methanone

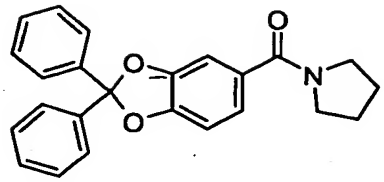


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 4-hydroxypiperidin hydrochloride (34 mg, 0.25 mmol) and ethyl-diisopropylamine (58 mg, 0.45 mmol), the title compound was obtained as a colorless foam (73 mg, 91 %). Work up: after addition of water (20 ml), the reaction was stirred for 1 hour at room temperature. Methylene chloride was added and the mixture was stirred for further 10 minutes. The organic layer was separated, washed with water and dried over sodium sulfate. The solvent was evaporated to yield the product after drying at high vacuum.

MS (ISP): 402.5 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.51-7.56 (m, 4H), 7.43-7.49 (m, 6H), 7.07 (d, 1H), 7.05 (s, 1H), 6.91 (d, 1H), 4,76 (d, 1H, OH), 3.70 (m, 1H), 3.11-3.18 (m, 2H), 2.51 (m, 2H under the DMSO peak), 1.63-1.79 (m, 2H), 1.25 – 1.39 (m, 2H).

Example 52

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-pyrrolidin-1-yl-methanone

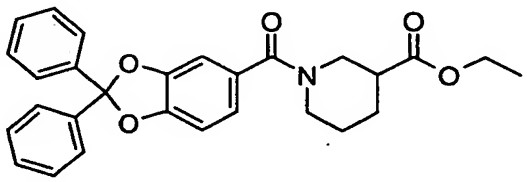


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), pyrrolidin (18 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol), the title compound was obtained as a light yellow foam (75 mg, 91 %). Work up: after addition of water (20 ml), the reaction was stirred for 1 hour at room temperature. Methylene chloride was added and the mixture was stirred for further 10 minutes. The organic layer was separated, washed with water and dried over sodium sulfate. The solvent was evaporated to yield the product after drying at high vacuum.

MS (ISP): 372.3 ($M+H^+$, 100), 743.3 ($2M+H^+$, 80). NMR (300 MHz, DMSO-D_6) ppm: 7.48-7.56 (m, 4H), 7.43-7.48 (m, 6H), 7.18 (s, 1H), 7.09 (d, 1H), 7.05 (d, 1H), 3.35-3.42 (m, 4H), 1.77-1.84 (m, 4H).

Example 53

Preparation of racemic 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidine-3-carboxylic acid ethyl ester



Method F

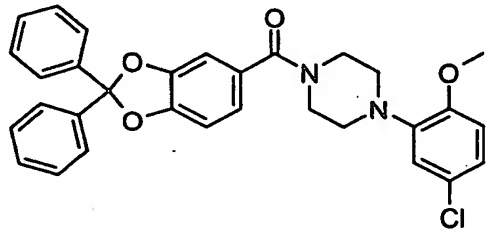
2,2-Diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), (rac)-ethyl nipecotate (36 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol) were dissolved in acetonitrile (1 ml) and stirred at room temperature over night. The reaction mixture was purified by preparative HPLC (acetonitrile/water 0.1 % formic acid as gradient) to yield the product as a white solid (24.8 mg, 27 %).

MS (ISP): 458.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.56 (m, 4H), 7.43-7.46 (m, 6H), 7.08 (d, 1H), 7.07 (s, 1H), 6.92 (d, 1H), 4.03 (m, 2H), 3.12 (m, 2H), 2.50 (m, 2H, under DMSO peak), 1.92 (m, 1H), 1.63 (m, 2H), 1.43 (m, 2H), 1.12 (m, 3H).

The following examples were prepared according to the above described method F:

Example 54

Preparation of [4-(5-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone

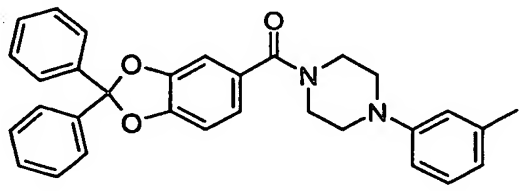


From 2,2-Diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(5-chloro-2-methoxy-phenyl)piperazin hydrochloride (66 mg, 0.25 mmol) and ethyl-diisopropylamine (64 mg, 0.50 mmol), the title compound was obtained as a white solid (42.7 mg, 41 %).

MS (ISP): 527.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.44-7.60 (m, 10H), 6.87-7.01 (m, 6H), 3.78 (s, 3H), 3.06 (br m, 4H), 2.97 (br m, 4H).

Example 55

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-m-tolyl-piperazin-1-yl)-methanone

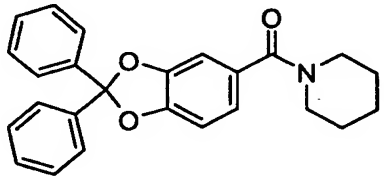


From 2,2-Diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(3-tolyl)piperazine dihydrochloride (62 mg, 0.25 mmol) and ethyl-diisopropylamine (96 mg, 0.75 mmol), the title compound was obtained as a light yellow solid (14.0 mg, 15%).

MS (ISP): 477.3 ($M+H^+$,100). NMR (300 MHz, DMSO-d_6) ppm: 7.53-7.57 (m, 4H), 7.44-7.48 (m, 6H), 7.09-7.13 (m, 3H), 6.99 (d, 1H), 6.75 (m, 2H), 6.62 (d, 1H), 3.60 (br m, 4H), 3.12 (br m, 4H), 2.24 (s, 3H).

Example 56

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-methanone



Method G

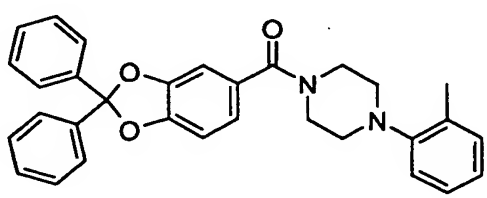
2,2-Diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (217 mg, 0.5 mmol), piperidine (46 mg, 0.55 mmol) and ethyl-diisopropylamine (0.1 ml, 0.6 mmol) were dissolved in methylene chloride (10 ml). The solution was stirred at room temperature for 4 hours and the solvent was evaporated. The residue was purified by column chromatography on silica gel (20 g, ethyl acetate eluant) to yield the product as a white solid (135 mg, 70%).

MS (ISP): 386.4 ($M+H^+$, 100), 771.3 ($2M+H^+$, 25). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.56 (m, 4H), 7.43-7.48 (m, 6H), 7.07 (d, 1H), 7.04 (s, 1H), 6.90 (d, 1H), 3.40 (br m, 2H), 1.58 (br m, 2H), 1.48 (br m, 6H).

The following examples were prepared according to method G:

Example 57

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-o-tolyl-piperazin-1-yl)-methanone

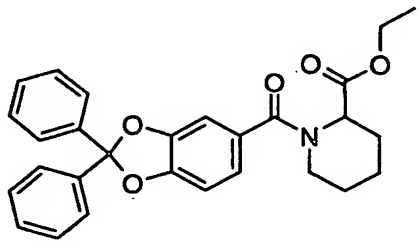


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(2-tolyl)piperazine dihydrochloride (62 mg, 0.25 mmol) and ethyl-diisopropylamine (96 mg, 0.75 mmol), the title compound was obtained as a light yellow solid (1.1 mg, 1%).

MS (ISP): 477.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.53-7.57 (m, 4H), 7.44-7.47 (m, 6H), 7.09-7.14 (m, 4H), 6.91-7.03 (m, 3H), 3.61 (br m, 4H), 2.82 (br m, 4H), 2.26 (s, 3H).

Example 58

Preparation of racemic 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidine-2-carboxylic acid ethyl ester

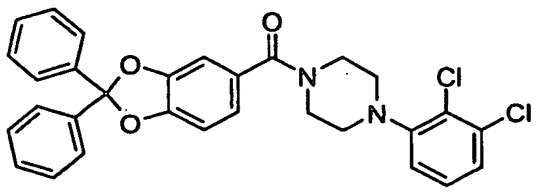


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), racemic ethyl pipecolinate (39 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol), the title compound was obtained as a white solid (22.6 mg, 24%).

MS (ISP): 458.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.53-7.56 (m, 4H), 7.43-7.49 (m, 6H), 7.09 (d, 1H), 7.02 (s, 1H), 6.92 (d, 1H), 5.14 (br m, 1H), 4.16 (br q, 2H), 3.58 (br m, 1H), 3.12 (br m, 1H), 2.11 (br m, 1h), 1.18-1.63 (m, 9 H).

Example 59

Preparation of [4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone

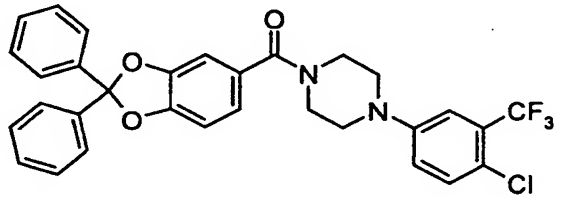


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(2,3-dichlorophenyl)piperazin hydrochloride (66.9 mg, 0.25 mmol) and ethyl-diisopropylamine (64 mg, 0.50 mmol), the title compound was obtained as a light yellow solid (58.3 mg, 55%).

MS (ISP): 531.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.53-7.57 (m, 4H), 7.44-7.48 (m, 6H), 7.31-7.33 (m, 2H), 7.11-7.14 (m, 2H), 7.09 (d, 1H), 7.02 (d, 1H), 3.63 (br m, 4H), 2.98 (br m, 4H).

Example 60

Preparation of [4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone

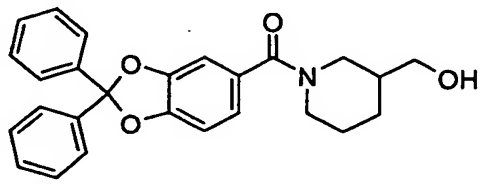


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(4-chloro-3-trifluoromethyl-phenyl)piperazin (66.2 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol), the title compound was obtained as a white solid (35.8 mg, 30%).

MS (ISP): 565.2 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.58 (m, 4H), 7.44-7.49 (m, 7H), 7.27 (s, 1H), 7.23 (d, 1H), 7.13 (s, 1H), 7.10 (d, 1H), 7.00 (d, 1H), 3.60 (br m, 4H), 3.28 (br m, 4H).

Example 61

Preparation of racemic (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(3-hydroxymethyl-piperidin-1-yl)-methanone

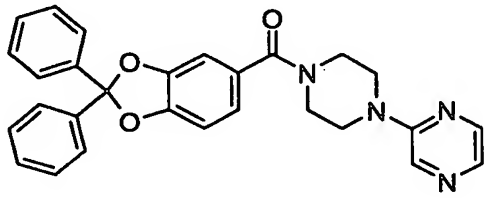


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), racemic 3-hydroxymethylpiperidin (28.8 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol), the title compound was obtained as a white solid (6.0 mg, 7%).

MS (ISP): 416.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 7.52-7.58 (m, 4H), 7.43-7.46 (m, 6H), 7.06 (d, 1H), 7.05 (s, 1H), 6.91 (d, 1H), 4.50 (br s, 1H, OH), 3.32 (m, 2H), 2.45 (m, 2H), 1.10-1.78 (m, 7H).

Example 62

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone

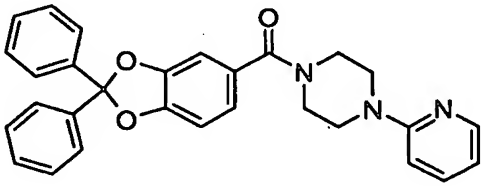


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(2-pyrazinyl)piperazine (41.1 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol), the title compound was obtained as a white solid (19.0 mg, 20%).

MS (ISP): 465.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 8.31 (s, 1H), 8.13 (s, 1H), 7.86 (s, 1H), 7.53-7.57 (m, 4H), 7.44-7.48 (m, 6H), 7.14 (s, 1H), 7.11 (d, 1H), 7.01 (d, 1H), 3.61 (br m, 8H).

Example 63

Preparation of (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone

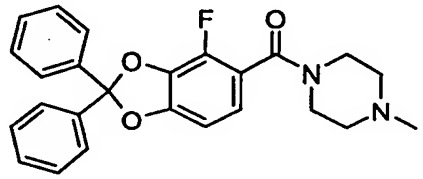


From 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (87 mg, 0.2 mmol), 1-(2-pyridyl)piperazine (40.8 mg, 0.25 mmol) and ethyl-diisopropylamine (32 mg, 0.25 mmol), the title compound was obtained as a white solid (53.2 mg, 57%).

MS (ISP): 464.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-d_6) ppm: 8.11 (m, 1H), 7.52-7.57 (m, 4H), 7.44-7.48 (m, 7H), 7.13 (s, 1H), 7.10 (d, 1H), 7.00 (d, 1H), 6.82 (d, 1H), 6.64 (dd, 1H), 3.53 (br m, 8H).

Example 64

Preparation of (4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone



Method H

4-Fluoro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (336 mg, 1 mmol) was dissolved in dichloromethane (15 ml). At room temperature EDCI (210 mg, 1.1. mmol) and 1-methyl-piperazine (220 mg, 2.2 mmol) were added and the solution was stirred for 5 hours at room temperature. The reaction was concentrated and the residue was chromatographied on silica gel (20 g, 5 % MeOH in CH_2Cl_2 eluant) to yield the product as white crystals (150 mg, 37 %).

MS (ISP): 419.4 ($M+H^+$, 100), 460.5 ($M+MeCN+H^+$, 70), 837.4 ($2M+H^+$, 50). NMR (300 MHz, DMSO-D_6) ppm: 7.52-7.58 (m, 4H), 7.46-7.50 (m, 6H), 7.01 (d, 1H), 6.92 (d, 1H), 3.60 (m, 2H), 3.22 (m, 2H), 2.32 (m, 2H), 2.22 (m, 2H), 2.18 (s, 3H).

Preparation of 4-Fluoro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid:

4-Fluoro-2,2-diphenyl-benzo[1,3]dioxole (5.8 g, 20 mmol) were dissolved in THF (40 ml). The reaction was cooled to –78°C under argon. TMEDA, (2.9 ml, 20 mmol) was added and then dropwise n-butyl lithium (12.5 ml, 1.6 N in hexane). After the addition the reaction was stirred at –78°C for 2 hours. Carbondioxide (20 g) was added at that temperature. The reaction was allowed to warm to 0°C and poured onto water (80 ml). The reaction was

extracted twice with ethyl acetate. The aqueous layer was neutralized with 1N aqueous HCl solution, extracted twice with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtered. The solvent was evaporated and the residue suspended in n-hexane, stirred for 10 minutes and the product was filtered off to yield the acid as a white solid (4.0 g, 60%). m.p.: 189-191°C.

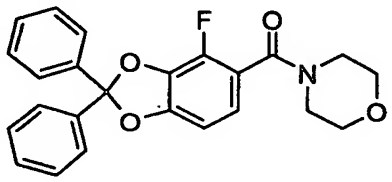
Preparation of 4-Fluoro-2,2-diphenyl-benzo[1,3]dioxole:

3-Fluorocatechol (12.81 g, 100 mmol) and dichlorodiphenylmethan (23.71 g, 100 mol) were dissolved in toluene (250 ml) and heated to reflux over night. The solvent was evaporated and the residue was chromatographied on silica gel (200 g, 1/1 CH_2Cl_2/n-hexane eluant) to yield the ketal as a white crystalline solid (26.74 g, 91 %). m.p.: 65-67°C.

The following examples were prepared using the method H:

Example 65

Preparation of (4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone

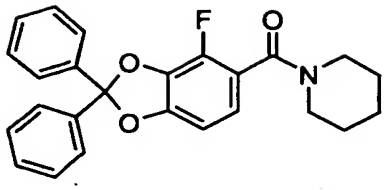


From 4-fluoro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (336 mg, 1 mmol), EDCI (210 mg, 1.1. mmol) and morpholine (190 mg, 2.2 mmol), the title compound was obtained as a white solid (183 mg, 46 %). Chromatography was performed on silica gel (20 g, 5 % MeOH in CH_2Cl_2 eluant).

MS (ISP): 406.4 ($M+H^+$, 100), 811.2 ($2M+H^+$, 25). NMR (300 MHz, DMSO-D_6) ppm: 7.54-7.58 (m, 4H), 7.46-7.50 (m, 6H), 7.01 (d, 1H), 6.96 (d, 1H), 3.63 (m, 4H), 3.52 (m, 2H), 3.27 (m, 2H).

Example 66

Preparation of (4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone

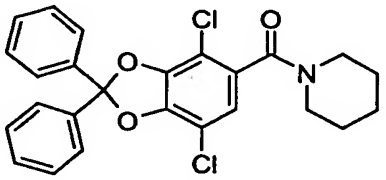


From 4-fluoro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (336 mg, 1 mmol), EDCI (210 mg, 1.1. mmol) and piperidine (187 mg, 2.2 mmol), the title compound was obtained as a white solid (103 mg, 26%). Chromatography was performed on silica gel (20 g, 5 % MeOH in CH_2Cl_2 eluant).

MS (ISP): 404.5 ($M+H^+$, 100), 807.4 ($2M+H^+$, 30). NMR (300 MHz, DMSO-D_6) ppm: 7.48-7.56 (m, 4H), 7.42-7.48 (m, 6H), 6.98 (d, 1H), 6.89 (d, 1H), 3.58 (m, 2H), 3.20 (m, 2H), 1.46-1.62 (m, 4H), 1.38-1.46 (m, 2H).

Example 67

Preparation of (4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone



From 4,7-dichloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (154 mg, 0.4 mmol), EDCI (84 mg, 0.44 mmol) and piperidine (75 mg, 0.88 mmol), the title compound was obtained as a white solid (27 mg, 15%). Chromatography was performed on silica gel (20 g, ethyl acetate eluant).

MS (ISP): 454.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.48-7.55 (m, 10H), 7.09 (s, 1H), 3.58 (m, 2H), 3.14 (m, 2H), 1.48-1.60 (m, 4H), 1.38-1.48 (m, 2H).

Preparation of 4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid:

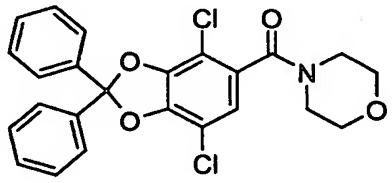
2,5-Dichloro-3,4-dihydroxybenzoic acid (1 g, 4.48 mmol) and dichlorodiphenylmethane (2.12 g, 9.96 mmol) are dissolved in toluene (40 ml) and heated to reflux for 24 hours. After cooling the solvent is evaporated and the residue is purified by column chromatography on silic agel (100g, CH_2Cl_2 then 5 % MeOH in CH_2Cl_2 eluant) to yield the acid as white crystals (490 mg, 28 %).

MS (ISN): 385.0 ($M-H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 13.47 (br s, 1H, OH), 7.59 (s, 1H), 7.54 (br m, 10 H).

The preparation of 2,5-Dichloro-3,4-dihydroxybenzoic acid is described in the literature (EP416410).

Example 68

Preparation of (4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone

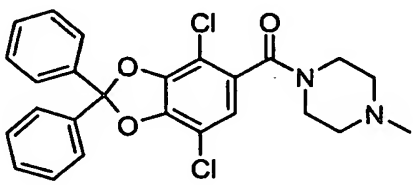


From 4,7-dichloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (154 mg, 0.4 mmol), EDCI (84 mg, 0.44 mmol) and morpholine (77 mg, 0.88 mmol), the title compound was obtained as a white solid (88 mg, 49%). Chromatography was performed on silica gel (20 g, ethyl acetate eluant).

MS (ISP): 456.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.52 (m, 10H), 7.15 (s, 1H), 3.45-3.72 (m, 6H), 3.20 (m, 2H).

Example 69

Preparation of (4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone

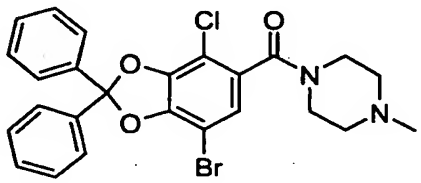


From 4,7-dichloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (115 mg, 0.3 mmol), EDCI (63 mg, 0.33 mmol) and N-methylpiperazine (66 mg, 0.66 mmol), the title compound was obtained as a white solid (28 mg, 20%). Chromatography was performed on silica gel (20 g, 5 % MeOH in CH_2Cl_2 eluant).

MS (ISP): 469.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.52 (m, 10H), 7.10 (s, 1H), 3.44-3.68 (m, 2H), 3.18 (m, 2H), 2.20-2.40 (m, 4H), 2.18 (s, 3H).

Example 70

Preparation of (7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone



From 7-bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (100 mg, 0.23 mmol), EDCI (49 mg, 0.25 mmol) and N-methylpiperazine (50 mg, 0.50 mmol), the title compound was obtained as a white solid (9 mg, 8%). Chromatography was performed on silica gel (20 g, 5% MeOH in CH_2Cl_2 eluant).

MS (ISP): 513.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.52 (m, 10H), 7.18 (s, 1H), 3.44-3.68 (m, 2H), 3.17 (m, 2H), 2.20-2.40 (m, 4H), 2.09 (s, 3H).

Preparation of 7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid:

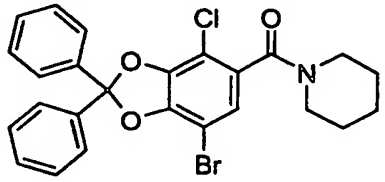
7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid methyl ester (520 mg, 1.16 mmol) is dissolved in THF (6 ml). Lithium hydroxid hydrate (190 mg, 4.64 mmol) in water (6 ml) is added. After addition of methanol (2 ml) the reaction is heated to reflux for 5 hours. After cooling the organic solvents are evaporated and the reaction is diluted with water, acidified with 1N aqueous HCl solution and extracted with ethyl acetate. The combined organic layers are washed with brine, dired over sodium sulfate and filtered. The solvent is evaporated in vacuo. The residue is stirred with n-hexane. The product precipitates as a white solid (350 mg, 70%), which is filtered and dried.

MS (ISP): 429.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 13.45 (br s, 1H, OH), 7.68 (s, 1H), 7.52 (m, 10H).

The preparation of 7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid methyl ester is described in the literature (EP 0 544 166).

Example 71

Preparation of (7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone

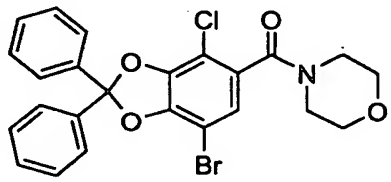


From 7-bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (100 mg, 0.23 mmol), EDCI (49 mg, 0.25 mmol) and piperidine (50 mg, 0.50 mmol), the title compound was obtained as a white solid (7 mg, 7%). Chromatography was performed on silica gel (20 g, ethyl acetate eluant).

MS (ISP): 498.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.52 (m, 10H), 7.17 (s, 1H), 3.56 (m, 2H), 3.12 (m, 2H), 1.48-1.60 (m, 4H), 1.40-1.482.09 (m, 2H).

Example 72

Preparation of (7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone

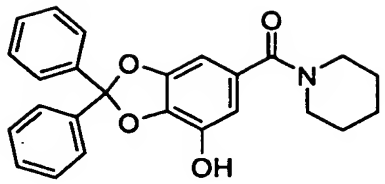


From 7-bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (1100mg, 0.23 mmol), EDCI (49 mg, 0.25 mmol) and morpholine (44 mg, 0.50 mmol), the title compound was obtained as a white solid (47 mg, 39 %). Chromatography was performed on silica gel (20 g, ethyl acetate eluant).

MS (ISP): 500.1 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.52 (m, 10H), 7.23 (s, 1H), 3.42-3.70 (m, 6H), 3.19 (m, 2H).

Example 73

Preparation of (7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone



Piperidine (0.3 ml, 2 mmol) and ethyl diisopropylamine (0.5 ml, 3 mmol) were dissolved in methylene chloride (10 ml). 7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxole-5-carbonyl chloride (353 mg, 1 mmol) dissolved in methylene chloride (3 ml) was added dropwise at room temperature. The reaction was stirred at room temperature for 24 hours. The solvenet was evaporated and the residue was partitionated between ethyl acetate and water. The organic layer was extracted with 1N aqueous HCl solution, brine, dried over sodium sulfate and filtered. The solvent was evaporated and the residue purified by column chromatography on silica gel (20 g, 5 % MeOH in CH_2Cl_2 eluant) to yield the phenol as a white solid (180 mg, 45 %).

MS (ISP): 400.3 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 10.08 (s, 1H, OH), 7.52-7.55 (m, 4H), 7.41-7.48 (m, 6H), 6.52 (s, 1H), 6.46 (s, 1H), 3.38 (br m, 4H), 1.59 (br m, 2H), 1.09 (br m, 4H).

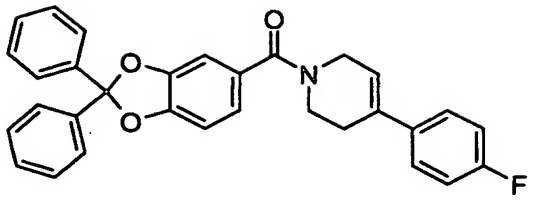
The preparation of 7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid is described in the literature (K. S. Feldman, S. M. Ensel, J. Am. Chem. Soc. 115 (3) (1993) 1162-3.)

Preparation of 7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxole-5-carbonyl chloride:

7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid (334 mg, 1 mmol) was dissolved in chloroform (5 ml). One drop of triethyl amine was added. At 45 to 50°C thionylchloride (0.33 ml, 4.5 mmol) was added within 30 minutes. The solution was than stirred for 6 hours at 70°C. The exccess thionyl chloride was removed by evaporation. The crude 7-hydroxy-2,2-diphenyl-benzo[1,3]dioxole-5-carbonyl chloride was used without further purification in the next step.

Example 74

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-carbonyl-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine

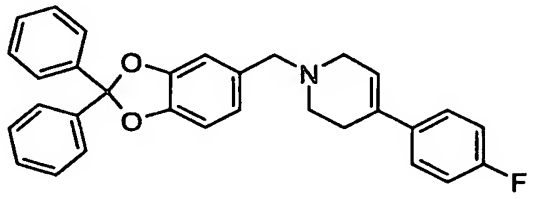


4-(4-Fluorophenyl)-1,2,3,4-tetrahydropyridin hydrochloride (106 mg, 0.5 mmol) was suspended in methylene chloride (10 ml). Ethyldiisopropyl amine (150 mg, 1.2 mmol) was added and then 2,2-diphenyl-benzo[1,3]dioxole-5-carboxylic acid benzotriazol-1-yl ester (150 mg, 0.5 mmol).The reaction was stirred for 2 hours at room temperature. The solvent was evaporated and the residue was purified by column chromatography on silica gel (20 g, ethyl acetate eluant). The amide was obtained as white crystals (177 mg, 75 %).

MS (ISP): 478.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.53-7.57 (m, 4H), 7.44-7.50 (m, 8H), 7.17 (t, 2H), 7.15 (s, 1H), 7.10 (d, 1H), 7.01 (d, 1H), 6.15 (br s, 1H), 4.15 (br s, CH_2), 3.62 (m, 2H), 2.52 (m, 2H under DMSO peak).

Example 75

Preparation of 1-(2,2-Diphenyl-benzo[1,3]dioxol-5-yl-methyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine



Lithium aluminium hydride (13 mg, 0.36 mmol) was suspended in THF (10 ml). At room temperature (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone (104 mg, 0.22 mmol) dissolved in THF (1.5 ml) was added dropwise under argon. The reaction was heated to reflux for 2 hours. Lithium aluminium hydride (50 mg) was added and the reaction was heated to reflux over night under argon. Lithium aluminium hydride solution (0.3 ml, 1M solution in THF) was added and the reaction heated to reflux for 4 hours. The reaction was cooled and under cooling (ice bath) and argon a mixture of water (0.4 ml) and THF (1.5 ml) was added carefully, slowly. The reaction was stirred for 10 minutes and solid potassium carbonate (2 g) was added. The reaction was filtered and the filtrate was concentrated in vacuo. The residue was dissolved

in ethyl acetate. The organic solution was dried over sodium sulfate, filtered and the solvent was evaporated to yield the product as a white colorless viscous oil (85 mg, 85 %).

MS (ISP): 464.4 ($M+H^+$, 100). NMR (300 MHz, DMSO-D_6) ppm: 7.52-7.56 (m, 4H), 7.42-7.53 (m, 7H), 7.14 (t, 2H), 6.98 (m, 2H), 6.87 (s, 1H), 6.83 (d, 1H), 6.09 (br s, 1H), 3.48 (s, CH_2), 3.01 (m, 2H), 2.59 (m, 2H), 2.52 (m, 2H).

Galenical Examples

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

The active ingredient is sieved and mixed with microcristalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidon in water. The granulate is mixed with sodium starch glycolate and magesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

The components are sieved and mixed and filled into capsules of size 2.

Example C

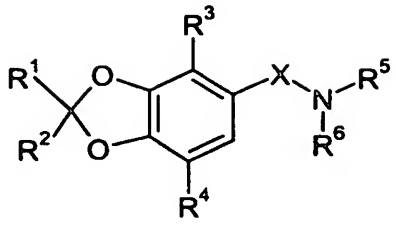
Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Claims

1. Compounds of formula (I)



(I)

wherein

R^1 and R^2 are independently phenyl, optionally mono-, di- or tri-substituted, independently, by hydroxy, lower alkyl, lower alkoxy, perfluoro-lower alkyl, alkanoyl, cyano or halogen;

R^3 and R^4 are independently hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, perfluoro-lower alkyl, alkanoyl or cyano;

R^5 is hydrogen or lower alkyl;

R^6 is phenyl or phenyl lower alkyl, wherein the phenyl moiety may optionally be mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxy, halogen, perfluoro-lower alkyl, hydroxy, alkanoyl or cyano;

R^5 and R^6 together with the nitrogen atom to which they are attached form a 5-, 6- or 7-membered monocyclic or a 9- or 10-membered bicyclic, saturated or unsaturated heterocyclic ring which may optionally contain one or two further heteroatoms independently selected from O, N and S, said heterocyclic ring being optionally mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxycarbonyl, hydroxy lower alkyl, alkanoyl, amino lower alkyl, hydroxy, (lower alkoxy, halogen, perfluoro-lower alkyl, cyano), heteroaryl, or by phenyl or phenyl lower alkyl, wherein the phenyl moiety may optionally be mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxy, halogen, perfluoro-lower alkyl, hydroxy, alkanoyl or cyano;

X is $-CH_2-$, $-C(O)-$ or $-SO_2-$;

and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^5 and R^6 together with the nitrogen atom to which they are attached form a heterocyclic ring selected from piperazinyl, morpholino, piperidinyl, piperidinone, pyrrolidinyl, isoquinolinyl, tetrahydro-pyridinyl, dioxa-azo-spirodecyl and diazepanyl, optionally mono-, di- or tri-substituted, independently, by lower alkyl, lower alkoxycarbonyl, hydroxy lower alkyl, aryl or heteroaryl.

3. Compounds according to any of claims 1 to 2, wherein aryl denotes phenyl, optionally mono-, di- or tri-substituted, independently, by hydroxy, halogen, lower alkyl, lower alkoxy, perfluoro-lower alkyl.

4. Compounds according to any of claims 1 to 3, wherein heteroaryl denotes benzodioxolyl, pyridinyl or pyrazinyl, optionally substituted by hydrogen, halogen, lower alkyl, lower alkoxy, perfluoro-lower alkyl.

5. Compounds according to any of claims 1 to 4, wherein X is $-SO_2-$.

6. Compounds according to any of claims 1 to 4, wherein X is –CO-.

7. Compounds according to any of claims 1 to 7, selected from the group consisting of:

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine,

1-(4-Chloro-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

1-(2,3-Dimethyl-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

1-(2,4-Dichloro-phenyl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(3-chloro-phenyl)-piperazine,

4-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-morpholine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-phenyl-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-pyrrolidine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(3-methoxy-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-methoxy-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-methoxy-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-chloro-phenyl)-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(2-fluoro-phenyl)-piperazine,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid phenethyl-amide,

1-Benzo[1,3]dioxol-5-yl-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperazine,

4-Benzyl-1-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-piperidine,

2-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid benzyl-methyl-amide,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid benzylamide,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-methyl-[1,4]diazepane,

1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-4-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-[1,4]diazepane,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid phenylamide,

2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonic acid [2-(4-methoxy-phenyl)-ethyl]-amide,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-methyl-piperazine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine,

4-(4-Chloro-phenyl)-1-(2,2-diphenyl-benzo[1,3]dioxole-5-sulfonyl)-1,2,3,6-tetrahydro-pyridine,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-sulfonyl)-4-phenyl-1,2,3,6-tetrahydro-pyridine,

racemic 1-[2-(2-Chloro-phenyl)-2-(4-methoxy-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(2-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(2-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-(4-methoxy-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

1-[2,2-Bis-(4-chloro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Fluoro-phenyl)-2-phenyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Methoxy-phenyl)-2-phenyl-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-p-tolyl-benzo[1,3]dioxole-5-sulfonyl]-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine,

racemic 1-[2-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(2,4-Dichloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

1-[2,2-Bis-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(3-Chloro-phenyl)-2-(4-fluoro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic 1-[2-(4-Chloro-phenyl)-2-(2-chloro-phenyl)-benzo[1,3]dioxole-5-sulfonyl]-piperidine,

racemic (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(3-hydroxy-pyrrolidin-1-yl)-methanone,

4-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperazine-1-carbaldehyde,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-hydroxymethyl-piperidin-1-yl)-methanone,

(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-isopropyl-piperazin-1-yl)-methanone,

1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidin-4-one,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-hydroxy-piperidin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-pyrrolidin-1-yl-methanone,

racemic 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidine-3-carboxylic acid ethyl ester,

[4-(5-Chloro-2-methoxy-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-m-tolyl-piperazin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-o-tolyl-piperazin-1-yl)-methanone,

racemic 1-(2,2-Diphenyl-benzo[1,3]dioxole-5-carbonyl)-piperidine-2-carboxylic acid ethyl ester,

[4-(2,3-Dichloro-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-(2,2-diphenyl-benzo[1,3]dioxol-5-yl)-methanone,

racemic (2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(3-hydroxymethyl-piperidin-1-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone,

(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-(4-pyridin-2-yl-piperazin-1-yl)-methanone,

(4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(4-Fluoro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(4,7-Dichloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-(4-methyl-piperazin-1-yl)-methanone,

(7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

(7-Bromo-4-chloro-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-morpholin-4-yl-methanone,

(7-Hydroxy-2,2-diphenyl-benzo[1,3]dioxol-5-yl)-piperidin-1-yl-methanone,

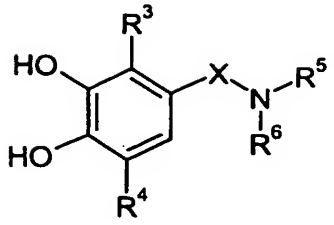
(2,2-Diphenyl-benzo[1,3]dioxol-5-yl)-[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-methanone, and

1-(2,2-Diphenyl-benzo[1,3]dioxol-5-ylmethyl)-4-(4-fluoro-phenyl)-1,2,3,6-tetrahydro-pyridine,

and pharmaceutically acceptable salts thereof.

8. A process for the manufacture of compounds of formula (I) as defined in any of claims 1 to 12, which process comprises:

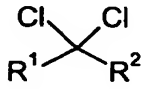
a) ketalizing a katechol intermediate of formula (A)



(A)

wherein R^2, R^3, R^4, R^5 and X are as defined in claim 1;

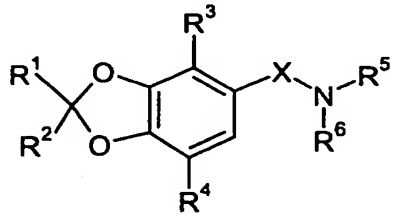
with a bis-substituted dichloromethane derivative of formula (B)



(B)

wherein R^1 and R^2 are as defined in claim 1;

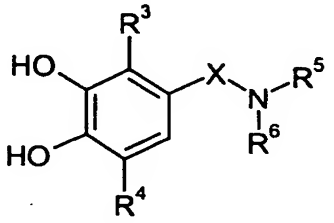
in an inert solvent or neat with or without the presence of a base at elevated temperature to produce a compound of formula (I)



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in claim 1;

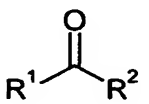
b) reacting the Katechol intermediate of formula (A)



(A)

wherein R^2, R^3, R^4, R^5 and X are as defined in claim 1;

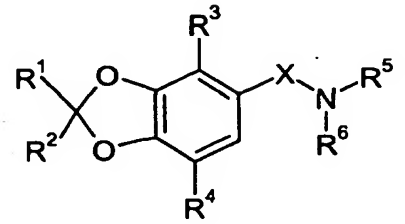
with a ketone of formula (C)



(C)

wherein R^1 and R^2 are as defined in claim 1;

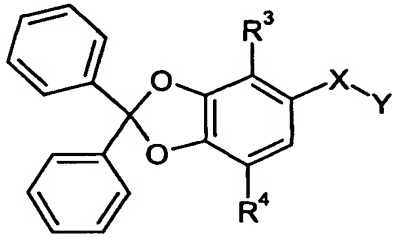
at elevated temperature neat or in an inert solvent with or without the removal of water by destillation, azeotropic destillation or addition of drying agents to produce a compound of formula (I)



(I)

wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined in claim 1; or

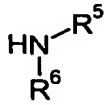
c) coupling a compound of formula (G)



(G)

wherein R^3 and R^4 are as defined in claim 1 and Y is Cl or OH when X is CO or Y is Cl when X SO_2;

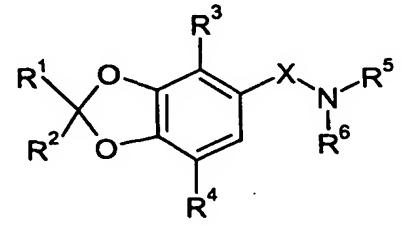
with an appropriate amine of formula (H)



(H)

wherein R^5 and R^6 are as defined in claim 1;

in a suitable inert solvent in the presence of a base and / or a coupling agent when X is CO and Y is OH to produce a compound of formula (I)



(I)

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claim 1 and X is CO or SO_2.

9. Compounds according to any of claims 1 to 12 when manufactured by a process according to claim 13.

10. Pharmaceutical compositions comprising a compound according to any of claims 1 to 12 and a pharmaceutically acceptable carrier and/or adjuvant.

11. Compounds according to any of claims 1 to 12 for use as therapeutic active substances.

12. Compounds according to any of claims 1 to 12 for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with modulation of the CB1 receptor.

13. A method for the treatment and/or prophylaxis of diseases which are associated with the modulation of the CB1 receptors which method comprises administering a compound according to any of claims 1 to 12 to a human being or animal.

14. The use of compounds according to any of claims 1 to 12 for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

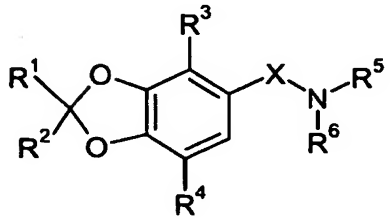
15. The use of compounds according to any of claims 1 to 12 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with the modulation of CB1 receptors.

16. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

***

Abstract

The present invention relates to compounds of formula (I)



wherein R^1, R^2, R^3, R^4, R^5 , R^6 and X are as defined in the description and claims, and pharmaceutically acceptable salts thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with the modulation ot CB1 receptors.

***